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Thiazolo[4,5-d]pyrimidinverbindungen zur Behandlung von rheumathoider Arthritis

Composés de thiazolo[4,5-d]pyrimidine pour le traitement de l'arthrite rhumatoïde

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(56) References cited:
EP-A- 0 778 277 **WO-A-00/09511**
WO-A-98/08847 **WO-A-99/51608**

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Description

[0001] The present invention relates to certain thiazolopyrimidinone compounds for use in the treatment of rheumatoid arthritis.

[0002] WO 98/08847 and EP0778277 each disclose a series of 6,5-hetero bicyclic compounds said to be useful as CRF antagonists.

[0003] Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

[0004] The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

[0005] The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

[0006] Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4 and CX3CR1. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

[0007] In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:

in which

R¹ represents a C₃-C₇ carbocyclic, C₁-C₈ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹ or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR³R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl or trifluoromethyl groups;

R² and R³, each independently represent a hydrogen atom, or a C₃-C₇ carbocyclic, C₁-C₈ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

(a) halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹;

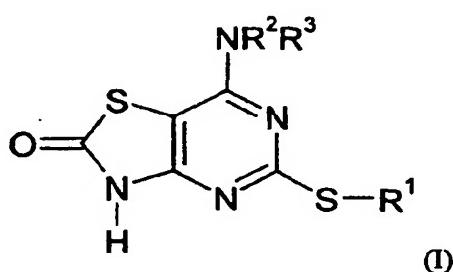
(b) a 3-8 membered ring optionally containing one or more atoms selected from O S, NR⁸ and itself optionally substituted by C₁-C₃-alkyl or halogen; or

(c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR⁹, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl and trifluoromethyl groups;

R⁴ represents hydrogen, C₁-C₆ alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹¹ and -NR¹²R¹³

R⁵ and R⁶ independently represent a hydrogen atom or a C₁-C₆ alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹⁴ and -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶ or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, -OR¹⁴, -COOR¹⁴, -



$\text{NR}^{15}\text{R}^{16}$, $-\text{CONR}^{15}\text{R}^{16}$, $-\text{NR}^{15}\text{COR}^{16}$, $-\text{SONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{SO}_2\text{R}^{16}$ or $\text{C}_1\text{-C}_6$ alkyl, itself optionally substituted by one or more substituents independently selected from halogen atoms and $-\text{NR}^{15}\text{SR}^{16}$ and $-\text{OR}^{17}$ groups;

R^{10} represents a hydrogen atom or a $\text{C}_1\text{-C}_6$ -alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, $-\text{OR}^{17}$ and $-\text{NR}^{15}\text{R}^{16}$; and

each of R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} independently represents a hydrogen atom or a $\text{C}_1\text{-C}_6$, alkyl, or a phenyl group; for use in the treatment of rheumatoid arthritis.

[0008] In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. Aryl groups include phenyl and naphthyl. Heteroaryl groups include 5- or 6-membered aromatic rings containing one or more heteroatoms selected from N, S, O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan.

[0009] Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

[0010] In formula (I) above, the group R^1 represents a $\text{C}_3\text{-C}_7$ carbocyclic, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl or $\text{C}_2\text{-C}_6$ alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, $-\text{OR}^4$, $-\text{NR}^5\text{R}^6$, $-\text{CONR}^5\text{R}^6$, $-\text{COOR}^7$, $-\text{NR}^8\text{COR}^9$, $-\text{SR}^{10}$, $-\text{SO}_2\text{R}^{10}$, $-\text{SO}_2\text{NR}^5\text{R}^6$, $-\text{NR}^8\text{SO}_2\text{R}^9$ or an aryl or heteroaryl group, both of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-\text{OR}^4$, $-\text{NR}^5\text{R}^6$, $-\text{CONR}^5\text{R}^6$, $-\text{COOR}^7$, $-\text{NR}^8\text{COR}^9$, $-\text{SR}^{10}$, $-\text{SO}_2\text{R}^{10}$, $-\text{SO}_2\text{NR}^5\text{R}^6$, $-\text{NR}^8\text{SO}_2\text{R}^9$, $\text{C}_1\text{-C}_6$ alkyl or trifluoromethyl groups. Particularly advantageous compounds of formula (I) are those in which R^1 represents an optionally substituted benzyl group. More preferably R^1 represents benzyl or benzyl substituted by one or more $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy or halogen atoms.

[0011] When R^2 and R^3 represent a group substituted by one or more 3-8 membered rings optionally containing one or more atoms selected from O, S or NR^8 , examples of such groups include piperidine, pyrrolidine, piperazine and morpholine.

[0012] Preferably one of R^2 and R^3 is hydrogen and the other is $\text{C}_1\text{-C}_8$ alkyl substituted by hydroxy and one or more methyl or ethyl groups. More preferably one of R^2 and R^3 is hydrogen and the other is $\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, $\text{CH}(\text{Et})\text{CH}_2\text{OH}$, $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$ or $\text{CH}(\text{CH}_2\text{OH})_2$. When

one of R^2 and R^3 is hydrogen and the other is $\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$ or $\text{CH}(\text{Et})\text{CH}_2\text{OH}$ the resulting compounds of formula (I) are preferably in the form of the (R) isomer.

[0013] Particularly preferred compounds for use in the invention include:

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, (*R*)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, (*R*)-7-[(2-Hydroxy-1-methylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-Difluorophenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethoxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxy-1-(hydroxymethyl)ethyl)amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 7-[(2-aminoethyl)amino]-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, *N*-[2-[[5-[(2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl] methanesulfonamide, (+/-)-5-[(2,3-difluorophenyl)methyl]thiol-7-[[2-(2-hydroxyethoxy)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 7-[[1*R*)-2-amino-1-methylethyl]amino]-5-[(2,3-difluorophenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-difluorophenyl)methyl]thio]-7-[[1*R*)-2-[(2-hydroxyethyl)amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-difluorophenyl)methyl]thio]-7-[[1*R*)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(3-Chloro-4-methoxyphenyl)methyl]thio]-7-[[1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(3-Chloro-2-fluorophenyl)methyl]thio]-7-[[1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-Difluorophenyl)methyl]thio]-7-[[3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 5-[(2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, 7-[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-[(2-

methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*-one,
 7-[[2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-
 5-[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-*d*]
 pyrimidin-2(3*H*-one,
 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[2-me-
 thyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[2-
 methylphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-
 2(3*H*-one,
 5-[(2-Furanyl)methyl]thio]-7-[[1*R*]-2-hydroxy-1-
 methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one,
 7-[[1*R*]-2-Amino-1-methylethyl]amino]-5-[[3-chlo-
 ro-2-fluorophenyl)methyl]thio] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one
 (2*S*)-2-[[5-[[2,3-Difluorophenyl)methyl]thio]-2,3-di-
 hydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-
 hydroxy-propanamide,
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-5-[(2-
 thiénylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one,
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-5-[[3-me-
 thyl-4-(methylsulfonyl)phenyl]methyl]thio]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one,
 5-[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]thio]-
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]
 pyrimidin-2(3*H*-one,
 5-[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]thio]-
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one,
 5-[[2,(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethyl-
 amino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one,
 5-[[2-fluorophenyl)methyl]thio]-7-[[1*R*]-2-hydroxy-
 1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one,
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-5-[[2-
 methoxyphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-5-[[2-phe-
 noxyethyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*-one,
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]-5-[[3-
 methylphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-
 2(3*H*-one,
 5-[[2-fluoro-3-methylphenyl)methyl]thio]-7-[[1*R*]-
 2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyri-
 midin-2(3*H*-one,
 5-[[3-chlorophenyl)methyl]thio]-7-[[1*R*]-2-hy-
 droxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 5-[[3-bromophenyl)methyl]thio]-7-[[1*R*]-2-hy-
 droxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 5-[[4-(difluoromethoxy)phenyl)methyl]thio]-
 7-[[1*R*]-2-hydroxy-1-methylethyl]amino]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one,

5 (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hy-
 droxy-1-(methoxymethyl)ethyl]amino]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one,
 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one,
 5-[[2-bromophenyl)methyl]thio]-7-[[1*R*]-2-hy-
 droxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 5-[[2,3-Difluorophenyl)methyl]thio]-7-[[1*R*]-2-hy-
 droxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[1*R*]-2-
 hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,
 (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hy-
 droxy-1-(methoxymethyl)ethyl]amino]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one,
 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one,
 7-[[1*R*]-2-Hydroxy-1-methylethyl]amino]-5-[(phe-
 nylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*-one,
 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-[[1*R*]-hy-
 droxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one,

and their pharmaceutically acceptable salts and sol-
 vates.

[0014] Particular salts of compounds of formula (I) in-
 clude:

5-[[2,3-Difluorophenyl)methyl]thio]-7-[[1*R*]-2-hy-
 droxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one sodium salt,
 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[1*R*]-2-
 hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimi-
 din-2(3*H*-one sodium salt,
 (+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-hy-
 droxy-1-(methoxymethyl)ethyl]amino]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one sodium salt,
 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one sodium salt, or
 7-[[1*R*]-2-Hydroxy-1-methylethyl]amino]-5-[(phe-
 nylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*-one
 sodium salt.

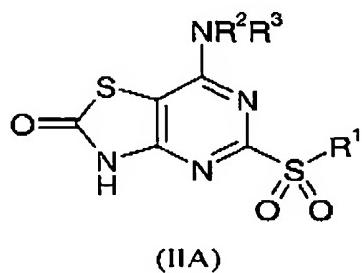
[0015] Further particular salts of compounds of formu-
 la (I) include:

7-[[1*R*]-2-amino-1-methylethyl]amino]-5-[[2,3-dif-
 luorophenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2
 (3*H*-one trifluoroacetate,
 5-[[2,3-difluorophenyl)methyl]thio]-7-[[1*R*]-2-[(2-
 hydroxyethyl)amino]-1-methylethyl]amino]thiazolo
 [4,5-*d*]pyrimidin-2(3*H*-one trifluoroacetate,
 5-[[2,3-difluorophenyl)methyl]thio]-7-[[1*R*]-

2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
 5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one trifluoroacetate,
 5-[[[2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one monohydrochloride, or
 5-[[[2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-d]pyrimidin-2(3H)-one dihydrochloride.

[0016] There is also provided a process for the preparation of a compound of formula (I) which comprises either:

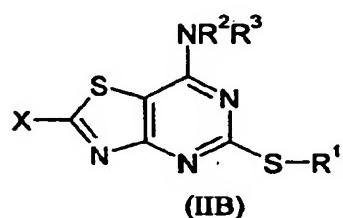
[0017] Treatment of a compound of formula (IIA)



where R¹, R² and R³ are as defined in formula (I) with a thiol R¹SH in the presence of a suitable base and optionally forming a pharmaceutically acceptable salt. The reaction may be carried out in a mixed solvent of DMSO and ethanol at a temperature between 0°C and 100°C using sodium borohydride as the base.

[0018] Compounds of formula (IIA) where R¹, R² and R³ are as defined in formula (I) may be prepared by treatment of compounds of formula (I) with a suitable oxidising agent such as oxone. The reaction may be carried out in a solvent such as acetonitrile at a temperature between 0°C and 100°C.

[0019] Or treatment of a compound of formula (IIB):



where R¹, R² and R³ are as defined in formula (I) and X is a leaving group with a metal alkoxide, followed by treatment with an acid or base and optionally forming a pharmaceutically acceptable salt.

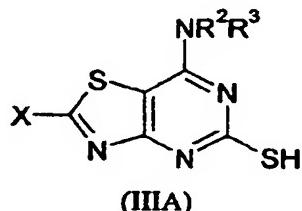
[0020] X is any suitable leaving group such as halogen.

The reaction may be carried out in an alcohol solvent such as methanol and the deprotection carried out in a solvent such as 1,4-dioxane. Examples of metal alkoxides include potassium methoxide. Examples of suitable acids include hydrochloric acid. Preferably the compound of formula (IIB) is treated with a metal alkoxide such as potassium methoxide followed by an acid such as conc. HCl in a solvent such as 1,4-dioxane.

[0021] Compounds of formula (IIB) where R¹, R² and R³ are as defined in formula (I) and X is a halogen, may be prepared from corresponding compounds (IIB) where R¹, R² and R³ are as defined in formula (I) and X is NH₂ by treatment with a diazotizing agent such as isoamylnitrite and a halogenating agent such as bromoform.

[0022] Compounds of formula (IIB) where R¹, R² and R³ are as defined in formula (I) and X is NH₂ may be prepared either by treatment of a compound of formula (IIIA):

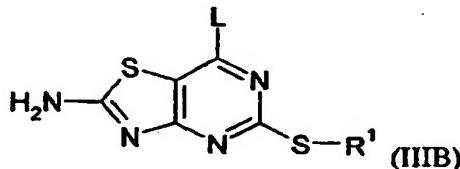
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30 where R² and R³ are as defined in formula (I) and X is NH₂ with a compound of formula R¹X where R¹ is as defined above and X is a leaving group such as bromide in the presence of a base such as diisopropylethylamine in an inert solvent such as DMSO/N-methylpyrrolidinone at a temperature between 0°C and 100°C.

[0023] Compounds of formula (IIIA) where R² and R³ are as defined in formula (I) and X is NH₂ may be prepared by treatment of a compound of formula (IIB) where R² and R³ are as defined in formula (I), X is NH₂ and R¹ is a suitable benzyl group such as benzyl or 2,3-difluorobenzyl with a reducing medium such as sodium metal in liquid ammonia, or by treatment of a compound of formula (IIIB):

45

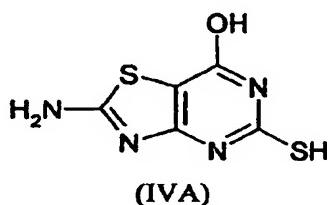


55 where R¹ is as defined in formula (I) and L is a leaving group such as chlorine with an amine HNR²R³ where R² and R³ are as defined in formula (I). The reaction may be carried out in a solvent such as N-methyl-pyrrolidine at a temperature between 0°C and 150°C. Compounds

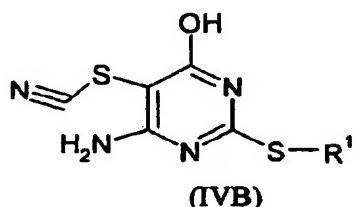
of formula (IIIB) where R¹ is as defined in formula (I) and L is a halogen may be prepared by treating a compound of formula (IIIB) where R¹ is as defined in formula (I) and L is a hydroxyl group with a halogenating agent such as phosphorous oxychloride.

[0024] The reaction may be carried out in the presence of dimethylaniline at reflux.

[0025] Compounds of formula (IIIB) where R¹ is as defined in formula (I) and L is a hydroxyl group may be formed either by treatment of a compound of formula (IVA) with a compound of formula R¹X where R¹ is as defined above and X is a leaving group such as bromide in the presence of a base such as potassium *tert*-butoxide in an inert solvent such as DMSO at ambient temperature.

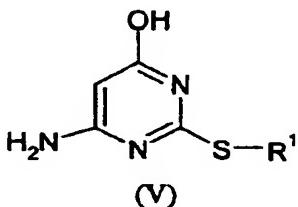


[0026] Or by heating a compound of formula (IVB) where R¹ is as defined above.

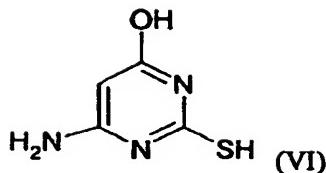


[0027] The reaction is preferably carried out in a suitable solvent such as DMF at elevated temperature, for example at about 120 °C.

[0028] Compounds of formula (IVB) may be readily prepared by reacting a compound of general formula (V) wherein R¹ is as defined above, with potassium thiocyanate and bromine in an inert solvent such as dimethylformamide/pyridine.



[0029] Compounds of formula (V) are suitably prepared by reacting a compound of formula (VI):



5 10 with a compound of formula R¹X where R¹ is as defined above and X is a leaving group such as bromide in the presence of a base such as sodium hydride in an inert solvent such as DMF at ambient temperature.

[0030] Compounds of formula (IVA) and (VI) are either commercially available or are well known in the literature.

[0031] It will be appreciated by those skilled in the art that in the processes described above the functional groups (e.g. hydroxyl groups) of intermediate compounds may need to be protected by protecting groups.

15 20 The final stage in the preparation of the compounds of the invention may involve the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmick. Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1991).

[0032] The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chlorprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

[0033] The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptors, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940

cluding rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitidés, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, and tumour metastasis;

(8) Diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC, diabetic retinopathy).

(9) Cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(10) Burn wounds & chronic skin ulcers

(11) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)

[0034] Thus, the present invention provides a com-

5 pound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in the treatment of rheumatoid arthritis.

[0035] Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CXC chemokine receptor subfamily, more preferably the target chemokine receptor is the CXCR2 receptor.

10 **[0036]** In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment of rheumatoid arthritis

15 **[0037]** In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of rheumatoid arthritis.

20 **[0038]** In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

25 **[0039]** For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

30 **[0040]** The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the 35 pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

40 **[0041]** The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

45 **[0042]** The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

50 **[0043]** The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or sus-

pensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compounds of the invention are administered orally.

[0044] The invention will now be further illustrated by reference to the following examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrix Silica 60[®](35-70 micron) or Prolabo Silica gel 60[®] (35-70 micron) suitable for flash silica gel chromatography. High pressure liquid chromatography purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson FC024 fraction collector or a Waters Delta Prep 4000. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulfoxide respectively.

Example 1

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

(a) Thiocysnic acid, 6-amino-1,4-dihydro-4-oxo-2-[(phenylmethyl)thio]-5-pyrimidinyl ester

[0045] 6-Amino-2-[(phenylmethyl)thio]4(1H)-pyrimidinone (10.5g)[preparation as described in WO 9635678] and potassium thiocyanate (25g) in N,N-dimethylformamide (200ml) were heated together at 65°C. Pyridine (6.3ml) was added and the solution cooled to 5°C. Bromine (2.2ml) was added slowly and the reaction mixture stirred for 2 hours at 5-10°C. The reaction mixture was poured onto ice water, stirred for 1 hour and the solid was isolated by filtration. After washing with water and ether, a pure sample was obtained after trituration with hot methanol.

MS (APCI) 291 (M+H, 100%).

(b) 2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7(4H)-one

[0046] The product of example 1 step a) (7.35g) was heated at 120°C in N,N-dimethylformamide (40ml)/water (10ml) for 10 hours. After cooling, the resulting solid was filtered off, washed with water, then ethyl acetate to give the subtitle compound.

m.p. 325°C

MS (APCI) 291 (M+H, 100%).

(c) 7-Chloro-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2-amine

[0047] The product from example 1 step b) (0.89g), phosphorus oxychloride (12ml) and N,N-dimethylaniline (1.2ml) were heated at reflux for 2 hours. The cooled reaction mixture was poured onto ice water and stirred for 2 hours. Chromatography (SiO₂, methanol/dichloromethane as eluant) gave the sub-title compound.
m.p. 217-218.5°C
MS (APCI) 309 (M+H, 100%).

(d) 2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0048] The product from example 1 step c) (0.6g) and 1-amino-2-methyl-propan-2-ol (1.1g) in tetrahydrofuran (10ml) was heated in a sealed vessel at 100 °C for 18 hours. The mixture was evaporated to dryness and purified (SiO₂, ethyl acetate as eluant) to give the subtitle compound (0.46g).
MS (APCI) 362 (M+H⁺ 100%).

(e) 2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0049] To a solution of the product from example 1 step d) (0.1g) in bromoform (5ml) was added isoamyl nitrite (0.13ml) and the mixture heated at 60 °C for 10 mins. The mixture was evaporated to dryness and purified (SiO₂, ethyl acetate: dichloromethane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.043g).
MS (APCI) 427 (M+H⁺, 100%).

(f) 2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0050] To a solution of the product from example 1 step e) (0.36g) in methanol (5ml) was added potassium hydroxide (0.095g) and the mixture stirred for 30 mins. The mixture was neutralised with concentrated hydrochloric acid then evaporated to dryness and purified (SiO₂, ethyl acetate: dichloromethane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.245g).

MS (APCI) 377 (M+H⁺, 100%).

(g) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-1-(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0051] To a solution of the product from example 1 step f) (0.21 g) in 1,4-dioxane (5ml) was added water (0.1ml) and concentrated hydrochloric acid (1 drop). The mixture heated at 45°C for 3 hours then evaporated to dryness. Recrystallisation (acetonitrile) gave the title compound (0.110g).
M.P 207-8 °C
MS (APCI) 363 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.37 (1H, s), 7.43-7.23 (5H, m), 6.61 (1H, bs), 4.81 (1H, t), 4.34 (2H, s), 3.55 (2H, bs), 1.32 (6H, s).

EXAMPLE 2

(R)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

(a) (R)-2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-1-butanol

[0052] To a mixture of the product of example 1 step c) (2.5g) and (R)-(-)-2-amino-1-butanol (5g) in a solvent of N-methylpyrrolidinone (10 ml) was added *N,N*-diisopropylethylamine (5 ml) and the resultant mixture heated at 100°C for 10 hours. The mixture was poured into water and the product collected by filtration to give the subtitle compound (2.5g)

MS (APCI) 362 (M+H⁺, 100%).

(b) (R)-2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-1-butanol

[0053] Prepared by the method of example 1 step e), using the product of example 2 step a).

MS (APCI) 427 (M+H⁺, 100%).

(c) (R)-2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-1-butanol

[0054] Prepared by the method of example 1 step f), using the product of example 2 step b).

MS (APCI) 377 (M+H⁺, 100%).

(d) (R)-7-[[1-(Hydroxymethyl)propyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0055] Prepared by the method of example 1 step g), using the product of example 2 step c).

M.P 217-8 °C

MS (APCI) 363 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.37 (1H, s), 7.43-7.21 (6H, m), 4.68 (1H, t), 4.32 (2H, q), 4.09 (1H, bs), 3.47-3.32 (2H, m), 1.69-1.59 (1H, m), 1.48-1.41 (1H, m), 0.82 (3H, t).

EXAMPLE 3

(R)-7-[[2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

(a) (R)-2-[[2-Amino-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-1-propanol

[0056] Prepared by the method of example 2 step a), using the product of example 1 step c) and (R)-(-)-2-amino-1-propanol.

MS (APCI) 412 (M+H⁺, 100%).

(b) (R)-2-[[2-Bromo-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-1-propanol

[0057] Prepared by the method of example 1 step e), using the product of example 3 step a) MS (APCI) 348 (M+H⁺, 100%).

(c) (R)-2-[[2-Methoxy-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-1-propanol

[0058] Prepared by the method of example 1 step f), using the product of example 3 step b) MS (APCI) 363 (M+H⁺, 100%).

(d) (R)-7-[[2-Hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0059] Prepared by the method of example 1 step g), using the product of example 3 step c).

MS (APCI) 349 (M+H⁺, 100%).
NMR δ H (d_6 -DMSO) 12.38 (1H, s), 7.44-7.20 (6H, m), 4.72 (1H, t), 4.32 (2H, m), 4.23 (1H, m), 3.49-3.29 (2H, m), 1.11 (3H, d).

EXAMPLE 4

5-[[((2,3-Difluorophenyl)methyl)thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0060] Potassium *t*-butoxide solution (0.45ml of 1M solution in tetrahydrofuran) was added to a stirred solution of 2-amino-5,6-dihydro-5-thioxo-thiazolo[4,5-d]pyrimidin-7(4H)-one (0.09g) [Cited: Indian J. Chem., Sect. B (1989), 28B(11), 964-5.] and 2,3-difluorobenzyl bromide in dimethyl sulphoxide (2ml). After stirring for 3 days, the reaction mixture was poured onto water to give and the subtitle compound, isolated by filtration.
MS (APCI) 327 (M+H⁺, 100%).

(b) 7-Chloro-5-[[((2,3-difluorophenyl)methyl)thio]thiazolo[4,5-d]pyrimidin-2-amine

[0061] Prepared by the method of example 1 step c), using the product of example 4 step a).

MS (APCI) 345 (M+H⁺, 100%).

(c) 2-[[2-Amino-5-[[((2,3-difluorophenyl)methyl)thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0062] Prepared by the method of example 2 step a), using the product of example 4, step b) and 2-amino-2-methylpropanol.

MS (APCI) 398 (M+H⁺, 100%).

(d) 2-[[2-Bromo-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0063] Prepared by the method of example 1 step e), using the product of example 4 step c).
MS (APCI) 462 (M+H⁺, 100%).

(e) 2-[[5-[(2,3-Difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0064] Prepared by the method of example 1 step f), using the product of example 4 step d).
MS (APCI) 413 (M+H⁺, 100%).

(f) 5-[(2,3-Difluorophenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0065] Prepared by the method of example 1 step f), using the product of example 4 step e).

MS (APCI) 399 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.41 (1H, s), 7.41-7.30 (2H, m), 7.21-7.13 (1H, m), 6.64 (1H, bs), 4.79 (1H, t), 4.41 (2H, s), 3.53 (2H, d), 1.29 (6H, s).

EXAMPLE 5

5-[(2,3-Difluorophenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) (2*R*)-2-[[2-Amino-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

[0066] Prepared by the method of example 2 step a), using the product of example 4 step b) and (R)-(-)-2-amino-1-propanol.

MS (APCI) 384 (M+H⁺, 100%).

(b) (2*R*)-2-[[2-Bromo-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

[0067] Prepared by the method of example 1 step e), using the product of example 5 step a).

MS (APCI) 448 (M+H⁺, 100%).

(c) (2*R*)-2-[[5-[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

[0068] Prepared by the method of example 1 step f), using the product of example 5 step b)

MS (APCI) 398 (M+H⁺, 100%).

(d) 5-[(2,3-Difluorophenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

5 [0069] Prepared by the method of example 1 step g), using the product of example 5 step c).
MS (APCI) 385 (M+H⁺, 100%).
NMR δ H (d_6 -DMSO) 12.41 (1H, s), 7.41-7.11 (4H, m), 4.72 (1H, t), 4.39 (2H, m), 4.21 (1H, m), 3.47-3.29 (2H, m), 1.09 (3H, d).

EXAMPLE 6

5-[(2,3-difluorophenyl)methyl]thio]-7-[(2-(hydroxyethoxy)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) 2-[2-[[2-amino-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethoxy]ethanol,

[0070] Prepared by the method of example 2 step a), using the product of example 4, step b) and 2-(2-aminoethoxy)-ethanol.

25 MS (APCI) 414 (M+H⁺, 100%).

(b) 2-[2-[[2-bromo-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethoxy]ethanol,

30 [0071] Prepared by the method of example 1 step e), using the product of example 6 step a).
MS (APCI) 478 (M+H⁺, 100%).

35 (c) 2-[2-[[5-[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethoxy]ethanol,

40 [0072] Prepared by the method of example 1 step f), using the product of example 6 step b).
MS (APCI) 429 (M+H⁺, 100%).

(d) 5-[(2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)ethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

45 [0073] Prepared by the method of example 1 step g), using the product of example 6 step c).
M.P 213-4 °C

50 MS (APCI) 415 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.41 (1H, s), 7.39-7.11 (4H, m), 4.57 (1H, t), 4.39 (2H, s), 3.57-3.38 (8H, m).

EXAMPLE 7

55

5-[[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(a) 2-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propane-diol,

[0074] Prepared by the method of example 2 step a), using the product of example 4, step b) and 2-amino-1,3-propandiol.

MS (APCI) 400 (M+H⁺, 100%).

(b) 2-[[2-Bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propane-diol,

[0075] Prepared by the method of example 1 step e), using the product of example 7 step a).

MS (APCI) 464 (M+H⁺, 100%).

(c) 2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propanediol,

[0076] Prepared by the method of example 1 step f), using the product of example 7 step b).

MS (APCI) 415 (M+H⁺, 100%).

d) 5-[[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

[0077] Prepared by the method of example 1 step g), using the product of example 7 step c).

M.P 178-9 °C

MS (APCI) 401 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.41 (1H, s), 7.42-7.11 (4H, m), 4.66 (2H, s), 4.40 (2H, s), 4.19 (1H,m), 3.49 (4H, m).

EXAMPLE 8

7-[(2-aminoethyl)amino]-5-[[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(a) 2-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]-carbamic acid, 1,1-dimethylethyl ester

[0078] Prepared by the method of example 2 step a), using the product of example 4, step b) and (2-aminoethyl)-carbamic acid, 1,1-dimethylethyl ester.

MS (APCI) 469 (M+H⁺, 100%).

b) [2-[[2-bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]-carbamic acid, 1,1-dimethylethyl ester

5 [0079] Prepared by the method of example 1 step e), using the product of example 8 step a).
MS (APCI) 533 (M+H⁺, 100%).

10 c) [2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethyl]-carbamic acid, 1,1-dimethylethyl ester

[0080] Prepared by the method of example 1 step f), using the product of example 8 step b).
15 MS (APCI) 489 (M+H⁺, 100%).

d) 7-[(2-aminoethyl)amino]-5-[[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

20 [0081] Prepared by the method of example 1 step g), using the product of example 8 step c).

M.P 215-6 °C

MS (APCI) 370 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.00 (1H, s), 7.45-7.11 (3H, m), 25 6.35 (1H,bs), 4.37 (2H, s), 3.48 (2H, m), 2.92 (2H, t),

EXAMPLE 9

5-[[[2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(a) 2-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethanol,

35 [0082] Prepared by the method of example 2 step a), using the product of example 4, step b) and ethanolamine
MS (APCI) 370 (M+H⁺, 100%).

(b) 2-[[2-bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethanol,

[0083] Prepared by the method of example 1 step e), using the product of example 9 step a).

MS (APCI) 434 (M+H⁺, 100%).

45

c) 2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]ethanol,

[0084] Prepared by the method of example 1 step f), using the product of example 9 step b).

MS (APCI) 385 (M+H⁺, 100%).

d) 5-[[[2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxyethyl)amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

55

[0085] Prepared by the method of example 1 step g), using the product of example 9 step c).

M.P 217-9 °C

MS (APCI) 371 (M+H⁺, 100%).
 NMR δH (d_6 -DMSO) 12.43 (1H, s), 7.67-7.64 (1H, m), 7.39-7.33 (2H, m), 7.16-7.12 (1H, m), 4.73 (1H, t), 4.40 (2H, s), 3.52-3.42 (4H, m).

EXAMPLE 10

N-[2-[[5-[(2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,

(a) **N-[2-[[2-amino-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

[0086] Prepared by the method of example 2 step a), using the product of example 4, step b) and *N*-[2-aminoethyl]- methanesulfonamide,
 MS (APCI) 448 (M+H⁺, 100%).

b) **N-[2-[[2-bromo-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

[0087] Prepared by the method of example 1 step e), using the product of example 10 step a).
 MS (APCI) 511 (M+H⁺, 100%).

c) **N-[2-[[5-[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-d]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

[0088] Prepared by the method of example 1 step f), using the product of example 10 step b).
 MS (APCI) 462 (M+H⁺, 100%).

d) **N-[2-[[5-[(2,3-difluorophenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,**

[0089] Prepared by the method of example 1 step g), using the product of example 10 step c).

M.P 225-6 °C
 MS (APCI) 448 (M+H⁺, 100%).

NMR δH (d_6 -DMSO) 12.49 (1H, s), 7.72 (1H, t), 7.41-7.13 (4H, m), 4.43 (2H, bs), 3.49 (2H, m), 3.13 (2H, m), 2.89 (3H, s).

EXAMPLE 11

(+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,

(a) **(+/-)-2-[2-[[2-amino-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]propoxy]ethanol,**

5 [0090] Prepared by the method of example 2 step a), using the product of example 4, step b) and (+/-)-2-aminopropoxy]ethanol,
 MS (APCI) 428 (M+H⁺, 100%).

10 b) **(+/-)-2-[2-[[2-bromo-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]propoxy]ethanol,**

[0091] Prepared by the method of example 1 step e), 15 using the product of example 11 step a).
 MS (APCI) 492 (M+H⁺, 100%).

c) **(+/-)-2-[2-[[5-[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-d]pyrimidin-7-yl]amino]propoxy]ethanol,**

[0092] Prepared by the method of example 1 step f), 20 using the product of example 1 step b).
 MS (APCI) 443 (M+H⁺, 100%).

25 d) **(+/-)-5-[[2,3-difluorophenyl)methyl]thio]-7-[[2-(2-hydroxyethoxy)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H-one,**

30 [0093] Prepared by the method of example 1 step g), using the product of example 11 step c).
 M.P 221-2 °C

MS (APCI) 429 (M+H⁺, 100%).
 NMR δH (d_6 -DMSO) 12.43 (1H, s), 7.47-7.30 (3H, m), 35 7.17-7.13 (1H, m), 4.56 (1H, t), 4.40 (2H, s), 4.35 (1H, m), 3.49-3.32 (6H, m), 1.10 (3H, d).

EXAMPLE 12

40 **7-[[[(1*R*)-2-amino-1-methylethyl]amino]-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one trifluoroacetate,**

45 (a) **(2*R*)-2-[[2-amino-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]propanamide,**

[0094] Prepared by the method of example 2 step a), 50 using the product of example 4, step b) and (2*R*)-2-amino-propanamide hydrochloride,
 MS (APCI) 397 (M+H⁺, 100%).

(b) **N-[(1*R*)-2-amino-1-methylethyl]-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-d]pyrimidine-2,7-diamine**

55 [0095] To a solution of the product from example 12 step a) (0.3 g) in dry tetrahydrofuran (10 ml) was added

2M borane in THF (10 ml) and the mixture heated under reflux for 6 hours. Quenched while hot with methanol (30 ml), evaporated to dryness and the residue taken up into methanol (30 ml) containing a few drops of concentrated hydrochloric acid. The mixture was then heated under reflux for a further 1 hour, evaporated to dryness to give a pale yellow solid.

MS (APCI) 383 (M+H⁺, 100%).

(c) [(2*R*)-2-[[2-amino-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl carbamic acid, 1,1-dimethylethyl ester

[0096] To a solution of the product from example 12 step b) (1.6 g) in THF (50 ml) was added diert-butyldicarbonate (0.91 g) and the mixture stirred for 2 days. Evaporated to dryness to give 2.0 g.

MS (APCI) 483 (M+H⁺, 100%).

(d) [(2*R*)-2-[[2-bromo-5-[(2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

[0097] Prepared by the method of example 1 step e), using the product of example 12 step c).

MS (APCI) 547 (M+H⁺, 100%).

(e) [(2*R*)-2-[[5-[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

[0098] Prepared by the method of example 1 step f), using the product of example 12 step d).

MS (APCI) 498 (M+H⁺, 100%).

(f) 7-[[(*1R*)-2-amino-1-methylethyl]amino]-5-[(2,3-difluorophenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

[0099] Prepared by the method of example 1 step g), using the product of example 12 step e) and purified by the method of example 15 step f).

MS (APCI) 384 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.55 (1H, s), 7.81 (3H, bs), 7.45-7.31 (4H, m), 7.18-7.13 (1H, m), 4.51-4.34 (3H, m), 2.95 (2H, m), 1.14 (3H, d).

EXAMPLE 13

5-[(2,3-difluorophenyl)methyl]thio]-7-[[(*1R*)-2-[(2-hydroxyethyl)amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

[0100] To a solution of the product from example 12 step f) (100 mg) in dry THF (5 ml) was added [(1,1-dimethylethyl)dimethylsilyloxy]-acetaldehyde (49 mg) followed by sodium triacetoxyborohydride (61 mg) and the mixture stirred for 1 hour. The mixture was acidified

with concentrated hydrochloric acid, stirred at room temp for 1 hour then evaporated to dryness. The product was purified (HPLC, Novapak® C18 column, 0.1% aqueous TFA:acetonitrile, gradient elution 75:25 to 5:95 over 15 minutes) to afford the title compound (0.021g). MS (APCI) 428 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 7.39-7.29 (2H, m), 7.17-12 (1H, m), 6.92 (1H, m), 4.91 (1H, s), 4.48-4.32 (3H, m), 3.54 (2H, m), 2.94-2.82 (4H, m), 1.12 (3H, m).

EXAMPLE 14

5-[(2,3-difluorophenyl)methyl]thio]-7-[[(*1R*)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

[0101] Prepared by the method of example 13 using the product of example 12, step f) and 40 % aqueous formaldehyde solution.

MS (APCI) 412 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.00 (1H, s), 7.39-7.31 (2H, m), 7.18-7.09 (2H, m), 4.39 (2H, q), 4.30 (1H, m), 3.31 (6H, bs), 2.43-2.38 (1H, m), 2.24-20 (1H, m), 1.07 (3H, d).

EXAMPLE 15

5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[(*1R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

(a) 2-(2-chloro-4-formylphenoxy)acetamide,

[0102] To a solution of 3-chloro-4-hydroxybenzaldehyde (10g) in methanol (100 ml) was added 1.0 M potassium t-butoxide (64 ml). To the mixture was added 2-chloroacetamide (5.96 g) and the mixture heated under reflux overnight. The mixture was evaporated to the residue triturated with water (500 ml) and the solid collected to give the subtitle compound (4.4g).

NMR δ H (CDCl₃) 9.89 (1H, s), 7.97 (1H, d), 7.82 (1H, dd), 7.04 (1H, d), 6.73 (1H, s), 5.87 (1H, s), 4.63 (2H, s).

(b) 2-[2-chloro-4-(bydroxymethyl)phenoxy]acetamide,

[0103] To a solution of the product from example 15 step a) (4.4g) in ethanol (500 ml) was added sodium borohydride (1.56 g) and the mixture allowed to stir for 1 hour. Acidified with glacial acetic acid, evaporated to dryness and extracted into ethyl acetate, washed with water to give the subtitle compound (4.3g).

NMR δ H (CDCl₃) 7.44 (1H, d), 7.29 (1H, d), 6.90 (1H, d), 6.81 (1H, s), 5.85 (1H, s), 4.63 (2H, s), 4.48 (2H, s), 1.96 (1H, s).

(c) 2-[4-[(acetylthio)methyl]-2-chlorophenoxy]acetamide,

[0104] Diisopropylazocarboxylate (5.5 ml) was added to a stirred solution of triphenylphosphine (7.31 g) in THF at 0 °C. Upon completion of addition a colourless precipitate deposited. To this suspension was added a mixture of the product from example 15 step b) (3.0 g) and thiol-acetic acid (2.00 ml) in THF (30 ml) at 0 °C. The mixture was allowed to attain room temp overnight, evaporated to dryness and the residue purified (SiO_2 , 10% ethyl acetate: 90% ether as eluant) to give the subtitle compound (3.5g).

NMR δH (CDCl_3) 7.35 (1H, d), 7.17 (1H, dd), 6.84 (1H, d), 6.76 (1H, s), 5.81 (1H, s), 4.54 (2H, s), 4.04 (2H, s), 2.35 (3H, s).

(d) 2-[2-chloro-4-(mercaptomethyl)phenoxy]acetamide,

[0105] To a solution of the product from example 15 step c)(1.0g) in methanol (50 ml) was added sodium hydroxide pellets (0.15 g) and the mixture stirred for 2 days. The mixture was diluted with water and the subtitle compound collected by filtration. (0.7 g).

NMR δH ($d_6\text{ DMSO}$) 7.44 (1H, s), 7.38 (1H, d), 7.21 (1H, dd), 6.98(1H, d), 4.55 (2H, s), 3.76 (2H, s).

(e) 7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]-5-[(phenylmethyl)sulfonyl]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

[0106] To a solution of the product from example 3 step d)(240 mg) in acetonitrile (100 ml) and water (100 ml) was added oxone (2.4 g) and the mixture heated at 40 deg for 2 hours. The acetonitrile was removed by rotary evaporation and the subtitle compound collected by filtration (235 mg)

MS (APCI) 381 ($M+\text{H}^+$, 100%).

(f) 5-[[[4-(2-aminoethoxy)-3-chlorophenyl]methyl]thio]-7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,

[0107] To a mixture of the product from example 15 step e) (100 mg), the product from example 15 step d) (329 mg) and sodium borohydride (50 mg) in a solution of DMSO (1 ml) and ethanol (10 ml) was heated at 55-60 °C for 12 hours. The reaction mixture was evaporated to dryness and the residue purified (HPLC, Nova-pak® C18 column, 0.1% aqueous TFA:acetonitrile, gradient elution 95:5 to 5:95 over 15 minutes) to afford the title compound (0.023g).

MS (APCI) 442 ($M+\text{H}^+$, 100%).

NMR δH ($D_2\text{O}$) 7.46 (1H, bs), 7.32 (1H, d), 7.00 (1H, d), 4.36-4.20 (5H, m), 3.61 (2H, m), 3.46 (2H, m), 1.20 (3H, d).

EXAMPLE 16

5-[[3-Chloro-4-methoxyphenyl)methyl]thio]-7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

a) 3-chloro-4-methoxybenzenemethanethiol

[0108] Thiourea (3.04g, 0.04 mol) was added to a solution of 3-chloro-4-methoxybenzyl bromide (4.0g, 0.02 mol) in ethanol (200 ml) and refluxed for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was subsequently dissolved in aqueous sodium hydroxide solution (30g, 0.75 mol in 300 ml water) and heated at 80 °C for one hour. The reaction mixture was cooled with an ice bath and acidified by addition of concentrated hydrochloric acid. The product was isolated by extraction three times into diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, to give the sub-title compound as a colourless oil in 83% yield (3.0g). NMR δH (CDCl_3) 7.34 (1H, m), 7.18 (1H, dd), 6.86 (1H, d), 3.89 (3H, s), 3.68 (2H, d), 1.76 (1H, t).

b) 5-[[3-Chloro-4-methoxyphenyl)methyl]thio]-7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0109] 3- chloro- 4- methoxybenzenemethanethiol (0.128g, 0.68 mmol), prepared in example 16 step a), the product of example 15 step e) (0.130g, 0.349 mmol), and sodium borohydride (0.026g, 0.68 mmol) were refluxed at 50 °C in a mixture of dimethylsulfoxide (6 ml) and ethanol (10 ml). After 3 hours and again after five hours reaction time, further portions of sodium borohydride (0.05g, 1.3 mmol) in ethanol (2 ml) were added to the reaction and reflux at 50 °C was continued until conversion was complete by hplc ms (15 hours in total). The reaction mixture was neutralised by addition of concentrated hydrochloric acid and the ethanol removed *in vacuo*. The residue was purified by reverse phase chromatography on Symmetry C8, eluting with a gradient of 25% to 95% acetonitrile in 0.1 M aqueous ammonium acetate over 10 minutes. The product was freeze dried from methanol/water/acetonitrile to obtain the sub-title compound in 33% yield as a white lyophylate (0.046g). MS (APCI) 413 ($M+\text{H}^+$, 100%). NMR δH ($d_6\text{ DMSO}$) 12.39 (1H, bs), 7.47 (1H, m), 7.36 (1H, m), 7.25 (1H, d), 7.06 (1H, d), 4.72 (1H, t), 4.32-4.21 (3H, m), 3.82 (3H, s), 3.49-3.30 (2H, m), 1.11 (3H, d).

EXAMPLE 17

5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*] pyrimidin-2(3*H*)-one

a) 3-chloro-2-fluorobzenemethanethiol

[0110] The sub-title compound was prepared as a colourless oil in 65% yield (2.51g) by the method described in example 16 step a) from 3-chloro-2-fluorobenzyl bromide (5.0g, 0.022 mol).

NMR δ H (CDCl_3) 7.32-7.21 (2H, m), 7.04 (1H, t), 3.75 (2H, d), 1.90 (1H, t).

b) 5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0111] The title compound was prepared by the method described in example 16 step b) from 3-chloro-2-fluorobzenemethanethiol, prepared in example 17 step a), and the product of example 15 step e).

The product was obtained in 12% yield as a white lyophilate (0.038g).

M.P 234.5 °C

MS (APCI) 401 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.4 (1H, bs), 7.55 (1H, m), 7.48 (1H, t), 7.26 (1H, d), 7.17 (1H, t), 4.72 (1H, bs), 4.38 (2H, m), 4.19 (1H, m), 3.3 (2H, m), 1.08 (3H, d).

EXAMPLE 18

5-[[2,3-Difluorophenyl)methyl]thio]-7-[[[(3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) 3-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-4-hydrory-(3*R*,4*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

[0112] (3*R*,4*R*)-3-Amino-4-hydroxy-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (0.73g), diisopropylethylamine (1.0 ml) and the product of example 4 step b), were stirred in NMP (10ml) at 100°C for 28hrs. The cooled mixture was poured onto water and the solid produced collected, washed with water and air dried. The crude material was purified (SiO_2 , ethyl acetate as eluant) to give the subtitle compound as a colourless solid (0.58g). m.p. 182-5°C

MS (APCI) 511 (M+H, 100%).

(b) 3-[[2-Bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-4-hydrory-(3*R*,4*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

[0113] Prepared by the method of example 1 step e), using the product of example 18 step a).

MS (APCI) 572 (M-H⁺, 100%).

(c) 3-[[5-[[2,3-Difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-4-hydroxy-(3*R*,4*R*)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

[0114] Prepared by the method of example 1 step f), using the product of example 18 step b).

MS (APCI) 526 (M+H⁺, 100%).

(d) -5-[[2,3-Difluorophenyl)methyl]thio]-7-[[[(3*R*,4*R*)-4-hydroxypyrrolidin-3-yl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0115] Prepared by the method of example 1 step g), using the product of example 18 step c). m.p. 270 °C (dec) MS (APCI) 412 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 7.32 (2H, m), 7.14 (1H, m), 6.46 (1H, d), 5.57 (1H, s), 4.39 (2H, s), 4.30 (2H, m), 3.39 (2H, m), 3.12 (1H, dd), 2.98 (1H, d).

EXAMPLE 19

25 5-[[2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one dihydrochloride

(a) 3-[[2-Amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3*R*-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

[0116] Prepared by the method of example 18 step a) using (3*R*)-3-amino-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester and the product of example 4 step b). MS (APCI) 495 (M+H⁺, 100%).

(b) 3-[[2-Bromo-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3*R*-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

[0117] Prepared by the method of example 1 step e), using the product of example 19 step a).

MS (APCI) 559 (M+H⁺, 100%).

(c) 3-[[5-[[2,3-Difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3*R*-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

[0118] Prepared by the method of example 1 step f), using the product of example 19 step b).

MS (APCI) 510 (M+H⁺, 100%).

(d) 5-[[2,3-Difluorophenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one, dihydrochloride

[0119] Prepared by the method of example 1 step g),

using the product of example 19 step c) then converted to the salt.

m.p. 178-181 °C

MS (APCI) 396 (M+H⁺, 100%).

NMR δH (d_6 -DMSO) 12.75 (1H,s), 9.19 (2H, bd), 7.91 (1H, d), 7.37 (2H, m), 7.17 (1H, m), 4.66 (1H, m), 4.43 (2H, dd), 3.10-3.50 (4H, m), 2.17 (1H, m), 1.96 (1H, m).

EXAMPLE 20

7-[[1*R*]-2-Hydroxy-1-methylethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]Pyrimidin-2(3*H*)-one

(a) **6-Amino-2-(((2-methyl-4-thiazolyl)methyl)thio)-4-(3*H*)-pyrimidinone**

[0120] 4- Amino-6-hydroxy-2-mercaptopurimidine hydrate (16.1g) and powdered sodium hydroxide (8.0g) was stirred in dry DMF (100ml) for 20 mins. 4-Chloromethyl-2-methylthiazole hydrochloride monohydrate (20g) was added portionwise and the resulting suspension stirred 18hrs. The mixture was poured onto water and the solid collected, washed with water and dried to afford the sub-title compound (24.3g)
MS (APCI) 255 (M+H⁺, 100%).

(b) **2-Amino-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7(6*H*)-one**

[0121] The product from example 20 step a) (24.3g) and potassium thiocyanate (37.1g) was stirred in dry DMF (400ml) with pyridine (13.1ml) at 0 °C. Bromine (4.5ml) was added over 1hr. After stirring 2hrs the mixture was poured into water. The resulting solution was concentrated to low volume then water added. The resulting solid was collected, taken up in 2M hydrochloric acid and precipitated by the addition of saturated sodium bicarbonate solution. The solid was collected, washed with water and dried to give the sub-title compound, (8.7g).
MS (APCI) 312 (M+H⁺, 100%).

(c) **7-Chloro-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2-amine**

[0122] Prepared by the method of example 1 step c), using the product of example 20 step b), (4.3g).
MS (APCI) 330/332 (M+H⁺), 330 (100%).

(d) **(2*R*)-2-[[2-Amino-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

[0123] Prepared by the method of example 18 step a), using the product of example 20 step c),
m.p. 220-2 °C
MS (APCI) 369 (M+H, 100%).

(e) **(2*R*)-2-[[2-Bromo-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

5 [0124] Prepared by the method of example 1 step e), using the product of example 20 step d).
MS (APCI) 433 (M+H⁺, 100%).

(f) **(2*R*)-2-[[2-Methoxy-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol**

[0125] Prepared by the method of example 1 step f), using the product of example 20 step e).
MS (APCI) 384 (M+H⁺, 100%).

(g) **7-[[1*R*]-2-Hydroxy-1-methylethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0126] Prepared by the method of example 1 step g), using the product of example 20 step f).
m.p. 208-9 °C
MS (APCI) 370 (M+H⁺, 100%).

25 NMR δH (d_6 -DMSO) 12.37 (1H, s), 7.35 (1H, s), 7.32 (1H, d), 4.73 (1H, t), 4.36 (2H, s), 4.21 (1H, m), 3.38 (2H, m), 2.62 (3H, s), 1.10 (3H, d).

EXAMPLE 21

7-[[2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*] pyrimidin-2(3*H*)-one

30 (a) **2-[[2-amino-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol**

[0127] Prepared by the method of example 18 step a),
40 using the product of example 20 step c) and 2-amino-1,3-propanediol
m.p.158-160 °C
MS (APCI) 385 (M+H, 100%).

45 (b) **2-[[2-Bromo-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol**

[0128] Prepared by the method of example 1 step e),
50 using the product of example 21 step a).
MS (APCI) 448 (M+H⁺, 100%).

(c) **2-[[2-Methoxy-5-[[[(2-methyl-4-thiazolyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-7-yl]amino]- 1,3-propanediol**

[0129] Prepared by the method of example 1 step f),
55 using the product of example 21 step b).

MS (APCI) 400 (M+H⁺, 100%).

(d) 7-[(2-Hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0130] Prepared by the method of example 1 step g), using the product of example 21 step c). m.p. 239-243°C
MS (APCI) 386 (M+H⁺, 100%).

NMR δH (d_6 -DMSO) 12.37 (1H,s), 7.38 (1H,s), 7.24 (1H, d), 4.67 (2H,t), 4.36 (2H, s), 4.20 (1H, m), 3.50 (4H, m), 2.62 (3H, s).

EXAMPLE 22

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

(a) 2-[[2-Amino-5-[[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0131] Prepared by the method of example 18 step a), using the product of example 20 step c) and 2-amino-2-methylpropanol
m.p. 250-252°C
MS (APCI) 383 (M+H, 100%).

(b) 2-[(2-Bromo-5-[[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0132] Prepared by the method of example 1 step e), using the product of example 22 step a).
MS (APCI) 446 (M+H⁺, 100%).

(c) 2-[[2-Methoxy-5-[[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-d]pyrimidin-7-yl]amino]-2-methyl-1-propanol

[0133] Prepared by the method of example 1 step f), using the product of example 22 step b).
MS (APCI) 398 (M+H⁺, 100%).

(d) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[2-methyl-4-thiazolyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0134] Prepared by the method of example 1 step g), using the product of example 22 step c).
m.p. 231-2°C
MS (APCI) 384 (M+H⁺, 100%).
NMR δH (d_6 -DMSO) 12.36 (1H,s), 7.37 (1H,s), 6.61 (1H, bs), 4.80 (1H, t), 4.37 (2H, s), 3.55 (2H, d), 2.62 (3H, s), 1.31 (6H, s).

EXAMPLE 23

7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[2-methylphenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one.

(a) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[2-methylphenyl)sulphonyl]thiazolo[4,5-d]pyrimidin-2(3H)-one.

[0135] A stirred solution of the product from example 1 step g) (0.14g) in glacial acetic acid (30ml) was treated with peracetic acid (36/40 % in acetic acid, 2ml), stirred for 2h, then at 50°C for 1h. The solution was quenched with an excess of dimethyl sulphide and evaporated to give a gum.
MS (APCI) 395 (M+H⁺, 100%).

(b) 7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[[2-methylphenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one.

[0136] The product from example 23 step (a) was taken up in DMSO (1.73ml), treated with potassium t-butoxide and divided into 3 portions. One portion was treated with 2-methylphenylmethyl mercaptan (0.053g), stirred at 50°C for 1h for 2h, neutralised with glacial acetic acid and subjected to preparative reverse phase HPLC on a 19 x 50mm symmetry C8 column using 10 to 60% acetonitrile in 0.1 % aqueous ammonium acetate over 6 min at 20 ml/min to give the titled compound.

MS (APCI) 377 (M+H⁺, 100%).
NMR δH (d_6 -DMSO) 1.33 (s, 6H); 2.35 (s, 3H); 3.57 (d, 2H); 4.33 (s, 2H); 4.82 (t, 1 H); 6.57 (broad s, 1H); 7.12-7.20 (mult., 3H); 7.41 (d, 1H); 12.37 (broad s, 1H)

EXAMPLE 24

5-[(2-Furanyl methyl)thiol-7-1[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one

(a) 7-[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-1-phenylmethyl)sulphonyl]thiazolo[4,5-d]pyrimidin-2(3H)-one.

[0137] The subtitled compound was prepared from the product of example 3 step d), using the method of example 23, step (a)
MS (ES) 381 (M+H⁺, 100%).

(b) 5-[(2-Furanyl methyl)thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one

[0138] The titled compound was prepared from the product of example 24 step (a), using the method of ex-

ample 23, step (b) using furfuryl mercaptan
MS (APCI) 339 (M+H⁺, 100%).
NMR δH (*d*₄-methanol) 1.12 (d, 3H); 3.41-3.45 (mult., 1H); 3.49-3.53 (mult., 1H); 4.24-4.32 (mult., 3H); 6.18-6.22 (mult., 2H); 7.29 (broad s, 1H).

EXAMPLE 25

7-[(1*R*)-2-Amino-1-methylethyl]amino]-5-[[[3-chloro-2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) [(1*R*)-2-amino-1-methyl-2-oxoethyl]carbamic acid, 9*H*-fluoren-9-ylmethyl ester

[0139] A solution of D-Alaninamide hydrochloride (3g) in 10% sodium carbonate solution (50 ml) and dioxane (50 ml) was treated with Fmoc chloride (6.24g) in dioxane (40 ml) and allowed to stir overnight. The mixture was diluted with water (500 ml) and the product collected by filtration and dried *in vacuo* to give 9.0g of the subtitle compound.

MS (ESI) BP 311 (+H)

(b) [(1*R*)-2-amino-1-methylethyl]carbamic acid, 9*H*-fluoren-9-ylmethyl ester

[0140] To a solution of the product from example 25 step a) (6.9g) in THF (100 ml) was added borane-methylsulfide complex (4.4 ml) and the mixture heated under reflux for 2 hours.

[0141] The mixture was carefully quenched by the addition of methanol (100 ml), evaporated to dryness and the residue taken up into methanol (100 ml) and acidified to pH 1-2 with concentrated hydrochloric acid. Heated under reflux for 30 mins then evaporated to dryness. The residue was triturated with ether to give a solid, which was collected by filtration, dissolved in water and the free base precipitated by the addition of aqueous sodium bicarbonate solution to give the subtitle compound (3.1g). MS (ESI) BP 297 (+H)

(c) (2*R*)-12-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-propyl]carbamic acid, 1,1-dimethylethylester.

[0142] To a stirred solution of the product from example 25 step b) (3.0g) in THF (100 ml) was added di-tert-butyl dicarbonate (2.2g) and the mixture stirred at room temp for 30 mins. The mixture was evaporated to dryness and the crude product purified (SiO₂, dichloromethane as eluant) to give the subtitle compound (3.8 g).

NMR δH (CDCl₃) 7.76 (2H, m), 7.42 (2H, m), 7.39-26 (4H, s), 5.01 (1H, s), 4.85 (1H, s), 4.38 (2H, d); 4.19 (1H, t), 3.77 (1H, m), 3.18 (2H, m), 1.27 (9H, s).

(d) [(2*R*)-2-aminopropyl]carbamic acid, 1,1-dimethylethylester

[0143] To a solution of the product from example 25 step c) (3.8g) in THF (100 ml) was added piperidine (5 ml) and the mixture allowed to stand for 1 hour at room temp. The mixture was evaporated to dryness and the residue purified (SiO₂, 5% methanol:dichloromethane as eluant) to give the subtitle compound as a colourless oil (1.7g).

NMR δH (CDCl₃) 4.95 (1H, s), 3.13 (1H, m), 2.99 (1H, m), 2.87 (1H, m), 1.38 (9H, s), 1.08 (3H, d).

(e) [(2*R*)-2-[[2-amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethylester

[0144] The product from example 1 step c) (2.0g) and the product from example 25 step d) (1.3g) in a solvent of NMP (10ml) containing Hunigs base (3 ml) was heated at 110 °C for 10 hours. The mixture was evaporated to dryness and purified (SiO₂, (1:1) dichloromethane:ethyl acetate as eluant) to give the subtitle compound (1.9g). MS (ESI) BP 447 (+H)

(f) [(2*R*)-2-[[2-amino-5-[(phenylmethyl)sulfonyl]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethylester

[0145] To a solution of OXONE (7.0g) in water (400 ml) was added sodium hydrogen carbonate until the pH was adjusted to 7.4. To this solution was added a solution of the product from example 25 step e) (1.9g) in acetonitrile (100 ml) and the mixture heated at 40 °C for 2 hours. Upon completion of the reaction the acetonitrile was removed by rotary evaporation to give the subtitle compound (1.7g). MS (ESI) BP 479 (+H)

(g) 3-chloro-2-fluoro-benzenemethanethiol,

[0146] A mixture of 3-chloro-2-fluorobenzylbromide (5.0g), thiourea (3.4 g) in a solvent of ethanol (200 ml) was heated under reflux for 16 hours. The mixture was evaporated to dryness and to the residue was added a solution of sodium hydroxide (30 g) in water (300 ml) and the mixture heated under reflux for 1 hour. Allowed to cool to room temperature and acidified with concentrated hydrochloric acid, the product was extracted into ether to give the subtitle compound as an oil (2.51 g).

NMR δH (CDCl₃) 7.32-21 (2H, m), 7.04 (1H, t), 3.75 (2H, d), 1.90 (1H, t).

(h) [(2*R*)-2-[[2-amino-5-[[3-chloro-2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethylester

[0147] To a mixture of the product from example 25

step f) (1.2g), the product from example 25 step g) (1.6 g) in a mixed solvent of ethanol (30 ml) and DMSO (5 ml) was added sodium borohydride (100 mg) and the mixture heated at 50 °C for 2 hours. The ethanol was removed by rotary evaporation and the crude product extracted into ethyl acetate and washed with water. The subtitle compound was obtained by purification (SiO₂, 1: 1)dichloromethane :ethyl acetate as eluant) to give (1.95g).

MS (ESI) BP 499 (+H)

(i) [(2*R*)-2-[[2-bromo-5-[[3-chloro-2-fluorophenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

[0148] Prepared by the method of example 1 step e), using the product of example 25 step h).

MS (APCI) 562 (M+H⁺, 100%).

(j) [(2*R*)-2-[[5-[[3-chloro-2-fluorophenyl]methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester

[0149] Prepared by the method of example 1 step f), using the product of example 25 step i).

MS (APCI) 514 (M+H⁺, 100%).

(k) 7-[[*(1R*)-2-Amino-1-methylethyl]amino]-5-[[3-chloro-2-fluorophenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-2-(3*H*)-one

[0150] Prepared by the method of example 1 step g), using the product of example 25 step j).

M.P 241-3 °C

MS (APCI) 400 (M+H⁺, 100%).

NMR δ_H (d₆-DMSO) 7.56 (1H, m), 7.49 (1H, m), 7.17 (1H, m), 7.05 (1H, bs), 4.44 (1H, m), 4.39 (2H, ab), 2.92 (2H, d), 1.13 (3H, d).

EXAMPLE 26

(2*S*)-2-[[5-[[2,3-Difluorophenyl]methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide

(a) (2*S*)-2-[[2-amino-5-[[2,3-difluorophenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide

[0151] The subtitled compound was prepared according to example 2 step (a) using the product of example 4 step b) (2g, 6 mmol), 1-serinamide (0.66g, 6 mmol), NMP (80 ml), and diisopropylethylamine (2 ml) to give the subtitled compound (1.36g)

Mp 145.151 °C

MS (APCI) 413 (M+H⁺, 100%).

NMR δ_H (d₆-DMSO) 8.10 (2H, bis). 7.40-7.07 (6H, m), 4.57 (1H, q), 4.43 (1H, d), 4.36 (1H, d), 3.71 (2H, d).

(b) (2*S*)-2-[[5-[[2,3-Difluorophenyl]methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-hydroxy-propanamide

5 [0152] Prepared by consecutive use of the methods of example 1 steps e), f), and g), using the product of example 26 step (a). The compounds formed during the separate steps were not purified or characterised. MS (APCI) 414 (M+H⁺, 100%).

10 NMR δ_H (d₆-DMSO) 12.47 (1H, br), 7.47 (1H, br), 7.42 (1H, s), 7.34 (2H, m), 7.13 (1H, m), 7.09 (1H, s), 4.90 (1H, t), 4.58 (1H, m), 4.39 (2H, m), 3.70 (2H, m).

EXAMPLE 27

7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]-5-[[2-thienylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-2-(3*H*)-one

20 a) 7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]-5-[[2-thienylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-2-(3*H*)-one

25 [0153] The title compound was prepared by the method described in example 16 step b) from the product of example 15 step e) (0.300g, 0.79mmol) and 2-thienylmethanethiol (0.32ml, 3.9mmol). The product was obtained in low 3% yield as a white lyophylate (0.010g).

30 MS (APCI) 355 (M+H⁺, 100%).

NMR δ_H (d₆-DMSO) 12.50 (1H, bs), 7.36 (1H, m), 7.16 (1H, bs), 7.07 (1H, m), 6.92 (1H, m), 4.72 (1H, bs), 4.55 (2H, d), 4.26 (1H, m), 3.44 (2H, m), 1.12 (3H, d).

35 EXAMPLE 28

7-[[*(1R*)-2-hydroxy-1-methylethyl]amino]-5-[[3-methyl-4-(methylsulfonyl)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

40 a) 3-methyl-4-(methylthio)benzaldehyde

45 [0154] Tin (IV) chloride (13.6ml, 0.116mol) was added to an ice-bath cooled solution of 1-methyl-2-(methylthio)benzene (10g, 0.073mol) in anhydrous dichloromethane (200ml) under nitrogen and stirred for a further 2 hours at 0 °C. α,α-Dichloromethyl methyl ether (6.56ml, 0.073mol) was introduced and the reaction stirred for 1 hour at <10 °C before the cooling was removed. After attaining room temperature, the reaction mixture was poured into ice/water (400ml), stirred and then extracted with dichloromethane (x3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated onto silica gel and purified by flash chromatography, eluting with diethyl ether / isohexane (10:1) to yield the sub-title compound as a brown oil (6.54g) in 54% yield.

GCMS 166 (M⁺, 100%).

NMR δ_{H} (CDCl_3) 9.91 (1H, s), 7.68 (1H, m), 7.62 (1H, s), 7.24 (1H, t), 2.54 (3H, s), 2.36 (3H, s).

b) 3-methyl-4-(methylthio)benzenemethanol

[0155] Sodium borohydride (1.40g, 0.037mol) was added to an ice-bath cooled solution of the product of example 28 step a) (6.16g, 0.037mol) in ethanol (50ml). After 1 hour, the reaction mixture was neutralised by careful addition of aqueous hydrochloric acid (2 molar) and concentrated *in vacuo* to remove the organic solvent. The remaining aqueous solution was then extracted with ethyl acetate (x3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to yield the sub-title compound as a brown oil (6g) in quantitative yield.

GCMS 168 (M⁺, 100%).

NMR δ_{H} (CDCl_3) 7.18 (3H, m), 4.62 (2H, bs), 2.46 (3H, s), 2.33 (3H, s).

c) 3-methyl-4-(methylsulfonyl)benzenemethanol

[0156] 3-chloroperoxybenzoic acid (57-86% grade, 20.4g) was stirred in dichloromethane (150ml), dried over anhydrous magnesium sulfate and then filtered. The filtrate was added dropwise over 1 hour to an ice-bath cooled, stirred solution of the product from example 28 step b) (5.67g, 0.034mol) in dichloromethane (50ml). The reaction mixture was filtered and the filtrate washed with aqueous sodium hydrogen carbonate solution followed by aqueous sodium dithionite solution (10g $\text{Na}_2\text{O}_4\text{S}_2$ in 150ml water). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* before purification by flash chromatography, eluting with dichloromethane/ methanol (100:2). The sub-title compound was obtained as a yellow oil (5.52g) in 82% yield.

MS (APCI) 201.1 (M+H⁺, 94.3%).

NMR δ_{H} (CDCl_3) 7.87 (1H, d), 7.38 (2H, m), 5.40 (1H, q), 4.56 (2H, d), 3.18 (3H, s), 2.61 (3H, s).

d) 3-methyl-4-(methylsulfonyl)benzenemethanethio acetate

[0157] Diethyl azodicarboxylate (4.33ml, 0.028mol) was added to an ice-bath cooled solution of triphenylphosphine (7.20g, 0.028mol) in tetrahydrofuran (40ml). To the resulting suspension was added a solution of the product from example 28 step c) (5.5g, 0.028mol) dissolved in tetrahydrofuran (20ml). After the precipitate had dissolved, thiolacetic acid was added to the reaction solution and the cooling was removed. After 16 hours at room temperature, the reaction was concentrated onto silica gel and purified by flash chromatography, eluting with isohexane / ethyl acetate (2:1). The sub-title compound was obtained as a pink solid (2.46g) in 35% yield. NMR δ_{H} ($d_6\text{-DMSO}$) 7.84 (1H, d), 7.36 (2H, m), 4.16 (2H, s), 3.19 (3H, s), 2.61 (3H, s), 2.37 (3H, s).

e) bis[[3-methyl-4-(methylsulfonyl)phenyl]methyl] disulfide

[0158] A mixture of the product of example 28 step d) (1.98g, 7.66mmol) and 7 molar methanolic/ammonia (30ml) was stirred for 24 hours. The product precipitated out of solution as a white solid and was isolated by filtration and dried *in vacuo*. The filtrate was similarly treated with 7 molar ammonia in methanol and yielded a second crop of solid, white product. In total, the sub-title compound was obtained in 32% yield (0.534g). MS (APCI) 451 (M+NH₄⁺, 98.9%). NMR δ_{H} ($d_6\text{-DMSO}$) 7.88 (2H, s), 7.38-7.34 (4H, m), 3.88 (4H, s), 3.20 (6H, s), 2.64 (6H, s).

f) 7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[[3-methyl-4-(methylsulfonyl)phenyl]methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0159] The title compound was prepared by the method described in example 16 step b) using the product from example 15 step e) (0.20g, 0.53mmol) and the product from example 28 step e) (0.34g, 0.79mmol) to yield 11% product as a white lyophylate (0.025g). MS (APCI) 441 (M+H⁺, 100%). NMR δ_{H} ($d_6\text{-DMSO}$) 12.40 (1H, s), 7.81 (1H, d), 7.52 (2H, m), 7.33 (1H, d), 4.74 (1H, t), 4.35 (2H, s), 4.19 (1H, m), 3.41 (1H, m), 3.34-3.28 (1H, m), 3.18 (3H, s), 2.61 (3H, s), 1.08 (3H, d).

EXAMPLE 29

5-[[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

a) 3-chloro-4-(trifluoromethoxy)benzenemethanethiol

[0160] To a solution of 3-chloro-4-(trifluoromethoxy)benzylbromide (5g) in ethanol (100 ml) was added thiourea (5g) and the mixture heated under reflux for 2 hours. The mixture was evaporated to dryness and the residue taken up into water (100 ml). To this solution was added sodium hydroxide pellets (3 g) and the mixture heated under reflux for 1 hour. The mixture was allowed to cool to room temperature and acidified with concentrated hydrochloric acid, the mixture was extracted with ether, dried and evaporated to give the subtitle compound as a colourless waxy solid (3.5g). NMR δ_{H} (CDCl_3) 7.35-7.09 (3H, m), 3.58 (2H, s).

b) 5-[[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0161] The title compound was prepared by the method described in example 16 step b) using the product

from example 15 step e) (0.40g, 1.05mmol) and the product from example 29 step a) (0.71g, 1.5mmol) to yield 10% product as a white lyophylate (0.046g).

MS (APCI) 467 (M+H⁺, 100%).

NMR δ_{H} (d_6 -DMSO) 12.42 (1H, s), 7.75 (1H, m), 7.52 (2H, m), 7.43 (1H, d), 4.72 (1H, t), 4.34 (2H, d), 4.18 (1H, quintet), 3.46-3.27 (2H, m), 1.07 (3H, d).

EXAMPLE 30

5-[[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

a) 2-fluoro-3-(trifluoromethyl)benzenemethanethiol

[0162] The subtitle compound was prepared from 2-fluoro-(3-trifluoromethyl)benzylbromide (10 g) using the method of example 29 step a)

NMR δ_{H} (CDCl₃) 7.68-7.18 (3H, m), 3.74 (2H, s), 1.98 (1H, s).

b) 5-[[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0163] The title compound was prepared by the method described in example 16 step b) using the product of example 15 step e) (0.47g, 1.23mmol) and the product of example 30 step a) (0.775g, 3.7mmol) to yield 5% product as a white lyophylate (0.025g).

MS (APCI) 435 (M+H⁺, 100%).

NMR δ_{H} (d_6 -DMSO) 12.42 (1H, s), 7.92 (1H, t), 7.68 (1H, t), 7.35 (2H, m), 4.71 (1H, bs), 4.42 (2H, m), 4.16 (1H, quintet), 3.40-3.30 (2H, m), 1.07 (3H, d).

EXAMPLE 31

5-[[(2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride

(a) 2-Bromo-7-chloro-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidine

[0164] The product of example 4 step (b) (8.0g) was suspended in bromoform (200ml) followed by addition of tert-butyl nitrite (8ml) and the whole heated at 60°C for 30 minutes. The solvents were removed by reduced pressure and the residue purified by column chromatography (silica- 1:1 dichloromethane/isohexane) to give a yellow solid (5.6g).

MS (APCI) 409/411 (M+H, 100%).

(b) 7-chloro-5-[(2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidine

[0165] The product of example 31 step a) (5.6g) was

suspended in methanol (150ml) and potassium hydroxide powder (0.77g) added. The whole was stirred at room temperature for 2 hours. The mixture was adjusted to pH 7 with a few drops of concentrated hydrochloric acid before it was evaporated to dryness. Purified by column chromatography (silica- 3:2 to 1:1 isohexane/dichloromethane) to give white solid (2.0g).

MS (APCI) 360/362 (M+H, 100%).

10 (c) 7-Chloro-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0166] The product from example 31 step (b) (2.0g) was dissolved in dioxan (150ml) followed by addition of concentrated hydrochloric acid (1ml) and water (1ml) and the whole heated at 40°C for 67 hours. The mixture was evaporated to dryness and purified by column chromatography (silica - dichloromethane) to give a white solid (1.4g).

20 MS (APCI) 346/348 (M+H, 100%).

(d) 5-[[2,3-difluorophenyl)methyl]thio]-7-[2-[(dimethylamino)ethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride

[0167] The product from example 31 step (c) (1.4g) was dissolved in dry tetrahydrofuran (5ml) and to the solution was added N,N-dimethylethylenediamine (0.25g) in a finger bomb which was heated at 80°C for 24 hours. The solvents were removed by reduced pressure and the residue partitioned between ethyl acetate and brine. The combined organic extracts were dried (sodium sulfate) and evaporated by reduced pressure for the ensuing residue to be purified by column chromatography (silica - 5:1 ethyl acetate/methanol) to give the free base as a sticky solid (0.095g). This was converted to the monohydrochloride by suspending the solid in methanol (10ml) followed by addition of concentrated hydrochloric acid (3 drops) to ensure dissolution then water (100ml) for the compound to be freeze dried to give a brown powder (0.080g).

m.p. 263°C(dec.)

MS (APCI) 398 (M+H, 100%).

NMR δ_{H} (d_6 -DMSO) 12.57 (1H,s), 10.22 (1H,s), 7.94(1H, t), 7.40(1H,m), 7.34(1H,m), 7.16(1H,m), 4.43(2H,s), 3.78 (2H,s), 3.21(2H,m), 2.78(6H,d)

EXAMPLE 32

5-[[2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) 2-[[2-amino-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2*R*-1-propanol

[0168] The product of example 1 step c) (25.0 g), D-Alaninol (12.3 g) and diisopropylethylamine (26.0 g)

were diluted in *N*-methylpyrrolidinone (250 ml) and stirred at 100 °C for 24 h before cooling and pouring the reaction mixture into H₂O (2.5 l). The precipitate was filtered and dried *in vacuo* before being preabsorbed onto silica gel. Chromatography using EtOAc, 4 % MeOH / EtOAc as eluents afforded the desired product as a yellow solid (9.0 g, 32 %).

MS (APCI) 347 (M+H, 100%).

(b) 2-[(2-amino-5-mercaptopthiazolo[4,5-*d*]pyrimidin-7-yl)amino]-(2*R*)-1-propanol

[0169] Sodium metal was added portionwise to a solution of the product of example 32 step a) (5.0 g) in ammonia (150 ml) until a blue colouration persisted. Ammonium chloride was then added and the solvent allowed to evaporate. The residue was dissolved in H₂O (200 ml) and filtered before neutralising with 2M HCl solution. The grey precipitate was filtered, washed with H₂O (200 ml) and dried *in vacuo* for 48 h to yield the subtitle compound as a brown solid (3.0 g).

MS (APCI) 258 (M+H, 100%).

(c) 2-[[2-amino-5-[(2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

[0170] 2-fluorobenzylbromide (0.369 g) was added portionwise to a solution of the product of example 32 step b) (0.5 g) and diisopropylethylamine (0.26 g) in DMSO / *N*-methylpyrrolidinone (4 ml / 0.5 ml) at 50 °C and stirring maintained for 1 h. The mixture was partitioned between H₂O (200 ml) and EtOAc (120 ml). The organics were recovered and washed further with H₂O (200 ml), dried over MgSO₄ and concentrated onto silica gel. The subtitle compound was purified by flash chromatography using DCM then EtOAc as eluents to yield a white solid (245 mg, 35 %).

MS (APCI) 366 (M+H, 100 %)

(d) 2-[[2-bromo-5-[(2-fluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

[0171] Isoamyl nitrite (0.3 ml) was added to a suspension of the product of example 32 step c) (0.23 g) in bromoform (15 ml) and acetonitrile (15 ml) at 50 °C. Stirring was maintained for 10 min before concentrating to approximately 3 ml. The residue was purified by column chromatography using 20 % EtOAc / DCM as eluent to yield the subtitle compound as a yellow solid (102 mg, 38 %).

MS (APCI) 429 (M+H, 100 %).

(e) 2-[[5-[(2-fluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

[0172] Potassium hydroxide (27 mg) was added to a solution of the product of example 32 step d) (0.1 g) in

MeOH (10 ml). The mixture was stirred for 24 h before neutralising to pH 7 with 2M HCl solution. The volatiles were removed *in vacuo* and the product used directly in the following step.

5 MS (APCI) 381 (M+H, 100 %).

(f) 5-[(2-fluorophenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

10 [0173] The product of example 32 step e) was dissolved in 1,4-dioxane (50 ml), H₂O (1 ml) and concentrated HCl solution (0.5 ml) and stirred for 20 h at 40 °C. The volatiles were removed under reduced pressure and the crude product purified by preparative HPLC to afford the subtitle compound as a white solid (21 mg).

15 MS (APCI) 367 (M+H, 100 %)
NMR δH (*d*₆-DMSO) 12.40 (1H, s), 8.14-7.11 (5H, m),
20 4.72 (1H, t), 4.35 (2H, m), 4.22 (1H, m), 3.47-3.29 (2H, m), 1.10 (3H, d)

EXAMPLE 33

7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-methoxyphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) 2-[[2-amino-5-[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

[0174] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 378 (M+H⁺, 100%).

(b) 2-[[2-bromo-5-[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

40 [0175] Prepared by the method of example 32 step d), using the product of example 33 step a).

MS (APCI) 441 (M+H⁺, 100%).

(c) 2-[[2-methoxy-5-[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol

[0176] Prepared by the method of example 32 step e), using the product of example 33 step b).

50 MS (APCI) 393 (M+H⁺, 100%).

(d) 7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-methoxyphenyl)methyl]thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

55 [0177] Prepared by the method of example 32 step f), using the product of example 33 step c).

MS (APCI) 379 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 7.40(1H, dd), 7.22 (1H, dt), 6.97 (1H, d), 6.84 (1H, dt), 6.00 (1H, d), 4.25 (2H, m), 4.15 (1H, m), 3.83 (3H, s), 3.48-3.31 (2H, m), 1.10 (3H, d).

EXAMPLE 34

7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) **2-[[2-amino-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0178] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 378 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol.**

[0179] Prepared by the method of example 32 step d), using the product of example 34 step a).

MS (APCI) 441 (M+H⁺, 100%).

(c) **2-[[2-methoxy-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0180] Prepared by the method of example 32 step e), using the product of example 34 step b).

MS (APCI) 393 (M+H⁺, 100%).

(d) **7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0181] Prepared by the method of example 32 step f), using the product of example 34 step c).

MS (APCI) 379 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.37 (1H, s), 7.30-7.26 (3H, m), 6.96-6.91 (3H, m), 4.71 (1H, t), 4.23-4.14 (3H, m), 3.46-3.28 (4H, m), 1.08 (3H, d)

EXAMPLE 35

7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) **2-[[2-amino-5-[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0182] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 362 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0183] Prepared by the method of example 32 step d),

using the product of example 35 step a).

MS (APCI) 425 (M+H⁺, 100%).

(c) **2-[[2-methoxy-5-[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0184] Prepared by the method of example 32 step e), using the product of example 35 step b).

MS (APCI) 377 (M+H⁺, 100%).

(d) **7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0185] Prepared by the method of example 32 step f), using the product of example 35 step c).

MS (APCI) 363 (M+H⁺, 100%).

NMR δ H (d_6 -DMSO) 12.37 (1H, s), 7.23-7.16 (4H, m), 7.04 (1H, d), 4.73 (1H, t), 4.28 (2H, m), 4.24 (1H, m), 3.48-3.30 (2H, m), 2.28 (3H, s), 1.11 (3H, d).

EXAMPLE 36

25 **5-[[[2-fluoro-3-methylpheriyl)methyl]thio]-7-[(1*R*)-2-hydrony-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

(a) **2-[[2-amino-5-[(2-fluoro-3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0186] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 380 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[(2-fluoro-3-methylphenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0187] Prepared by the method of example 32 step d), using the product of example 36 step a).

MS (APCI) 443 (M+H⁺, 100%).

45 (c) **2-[[5-[(2-fluoro-3-methylphenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-(2*R*)-1-propanol**

[0188] Prepared by the method of example 32 step e), using the product of example 36 step b).

MS (APCI) 395 (M+H⁺, 100%).

(d) **5-[[[2-fluoro-3-methylphenyl)methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0189] Prepared by the method of example 32 step f), using the product of example 36 step c).

MS (APCI) 381 (M+H⁺, 100%).
 NMR δH (d_6 -DMSO) 12.39 (1H, s), 7.37-7.00 (4H, m), 4.72 (1H, t), 4.33 (2H, m), 4.22 (1H, m), 3.47-3.30 (2H, m), 2.23 (3H, s), 1.11 (3H, d)

EXAMPLE 37

5-[[[3-chlorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) **2-[[2-amino-5-[[3-chlorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0190] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 382 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[[3-chlorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0191] Prepared by the method of example 32 step d), using the product of example 37 step a).

MS (APCI) 445 (M+H⁺, 100%).

(c) **2-[[5-[[3-chlorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0192] Prepared by the method of example 32 step e), using the product of example 37 step b).

MS (APCI) 397 (M+H⁺, 100%).

(d) **5-[[3-chlorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0193] Prepared by the method of example 32 step f), using the product of example 37 step c).

MS (APCI) 383 (M+H⁺, 100%).

NMR δH (d_6 -DMSO) 12.40 (1H, s), 7.49 (1H, d), 7.43-7.30 (4H, m), 4.72 (1H, t), 4.32 (2H, m), 4.21 (1H, m), 3.48-3.26 (2H, m), 1.09 (3H, d).

EXAMPLE 38

5-[[3-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) **2-[[2-amino-5-[[3-bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0194] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 426 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[[3-bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0195] Prepared by the method of example 32 step d), using the product of example 38 step a).
 MS (APCI) 491 (M+H⁺, 100%).

(c) **2-[[5-[[3-bromophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0196] Prepared by the method of example 32 step e), using the product of example 38 step b).
 MS (APCI) 443 (M+H⁺, 100%).

(d) **5-[[3-bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0197] Prepared by the method of example 32 step f), using the product of example 38 step c).

MS (APCI) 427 (M+H⁺, 100%).

NMR δH (d_6 -DMSO) 12.40 (1H, s), 7.63 (1H, t), 7.46-7.24 (4H, m), 4.72 (1H, t), 4.31 (2H, m), 4.21 (1H, m), 3.48-3.26 (2H, m), 1.10 (3H, d).

EXAMPLE 39

5-[[4-(difluoromethoxy)phenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) **2-[[2-amino-5-[[4-(difluoromethoxy)phenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0198] Prepared by the method of example 32 step c), using the product of example 32 step b).
 MS (APCI) 414 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[[4-(difluoromethoxy)phenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0199] Prepared by the method of example 32 step d), using the product of example 39 step a).
 MS (APCI) 477 (M+H⁺, 100%).

(c) **2-[[5-[[4-(difluoromethoxy)phenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-*(2R*)-1-propanol**

[0200] Prepared by the method of example 32 step e), using the product of example 39 step b).
 MS (APCI) 429 (M+H⁺, 100%).

(d) 5-[[[4-(difluoromethoxy)phenyl]methyl]thio]-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0201] Prepared by the method of example 32 step f), using the product of example 39 step c).

MS (APCI) 415 (M+H⁺, 100%).

NMR δ_H (*d*₆-DMSO) 12.38 (1H, s), 7.48 (2H, dt), 7.26 (1H, d), 7.19 (1H, t), 7.11 (2H, dd), 4.73 (1H, t), 4.31 (2H, m), 4.21 (1H, m), 3.47-3.30 (2H, m), 1.10 (3H, d)

EXAMPLE 40

(+/-)-5-[[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) (+/-)-2-amino-3-methoxy-1-propanol hydrochloride

[0202] To a suspension of DL- 3-methoxy-alanine (1.0g) in dry THF (100 ml) was added borane methyl-sulfide complex (10 ml) and the mixture heated under reflux for 16 hours. The mixture was then quenched with methanol while at reflux, evaporated to dryness and the residue taken up into methanolic hydrogen chloride (100 ml) and heated under reflux for a further 2 hours, evaporated to dryness to give the subtitle compound as a colourless gum (1.0g).

NMR δ_H (D₂O) 3.40 (3H, s), 3.53-3.74 (4H, m), 3.81 (1H, m)

(b) (+/-)-2-[[2-amino-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-methoxy-1-propanol,

[0203] Prepared by the method of example 12 step a) using the product of example 4 step b) and the product of example 40 step a).

MS (APCI) 414 (M+H⁺, 100%).

(c) (+/-)-2-[[2-chloro-5-[[2,3-difluorophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-methoxy-1-propanol,

[0204] To a solution of the product from example 40 step b) (1.0g) in a mixture of concentrated hydrochloric acid (40 ml) and water (32 ml) cooled in ice water was added a solution of sodium nitrite (0.4 g) in water (5 mL), stirred at this temp for 2 hours. The mixture was then extracted into ethyl acetate, dried and evaporated to give the subtitle compound (0.6g).

MS (APCI) 434 (M+H⁺, 100%).

(d) (+/-)-2-[[5-[[2,3-difluorophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-3-methoxy-1-propanol,

[0205] Prepared by the method of example 1 step f), using the product of example 40 step c).

MS (APCI) 429 (M+H⁺, 100%).

(e) (+/-)-5-[[[2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0206] Prepared by the method of example 1 step g), using the product of example 40 step d).

MS (APCI) 415 (M+H⁺, 100%).

EXAMPLE 41

20 7-[[2-hydroxy-4-(hydroxymethyl)ethyl]amino]-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

(a) 2-[[2-amino-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,

[0207] Prepared by the method of example 12 step a) using the product of example 1 step c) and 2-amino-1,3-propanediol.

MS (APCI) 364 (M+H⁺, 100%).

30 NMR δ_H (*d*₆-DMSO) 7.42-7.38 (1H, m), 7.28 (1H, t), 7.22 (1H, t), 5.30 (1H, d), 4.63 (1H, bs), 4.28 (2H, s), 4.03 (1H, m), 3.54-3.40 (4H, m).

(b) 2-[[2-chloro-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,

[0208] Prepared by the method of example 40 step c) and the product of example 41 step a)

MS (APCI) 384 (M+H⁺, 100%).

(c) 2-[[2-methoxy-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1,3-propanediol,

[0209] Prepared by the method of example 1 step f) and the product of example 41 step b)

MS (APCI) 379 (M+H⁺, 100%).

(d) 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

[0210] Prepared by the method of example 1 step g) and the product of example 41 step c) MS (APCI) 365 (M+H⁺, 100%).

EXAMPLE 42

5-[[2-(bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one

(a) **2-[[2-amino-5-[[2-(bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2*R*-1-propanol**

[0211] Prepared by the method of example 32 step c), using the product of example 32 step b).

MS (APCI) 428 (M+H⁺, 100%).

(b) **2-[[2-bromo-5-[[2-(bromophenyl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2*R*-1-propanol**

[0212] Prepared by the method of example 1 step e), using the product of example 42 step a).

MS (APCI) 491 (M+H⁺, 100%).

(c) **2-[[5-[[2-(bromophenyl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-2*R*-1-propanol**

[0213] Prepared by the method of example 1 step f), using the product of example 42 step b).

MS (APCI) 443 (M+H⁺, 100%).

(d) **5-[[2-(bromophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one**

[0214] Prepared by the method of example 1 step g), using the product of example 42 step c).

MS (APCI) 427 (M+H⁺, 100%).

NMR δH (*d*₆-DMSO) 12.41 (1H, s), 7.65-7.14 (5H, m), 4.72 (1H, t), 4.42 (2H, s), 4.21 (1H, m), 3.47-3.30 (2H, m), 1.10 (3H, d)

EXAMPLE 43

5-[[2,3-Difluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

[0215] The product from example 5 step d) was suspended in water and to this suspension was added 1 equivalent of 0.1 N sodium hydroxide solution, followed by the addition of a small aliquot of tetrahydrofuran to aid dissolution. The resultant solution was then lyophilised to give the title compound as a colourless solid.

MP 218-220 °C

MS (APCI) 385 (M+H⁺, 100%).

NMR δH (*d*₆-DMSO) 7.39-7.09 (3H, m), 5.60 (1H, d), 4.65 (1H, m), 4.34 (2H, q), 4.09 (1H, m), 3.44-3.27 (2H, m), 1.06 (3H, d).

EXAMPLE 44

5-[[3-Chloro-2-fluorophenyl)methyl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

5 **[0216]** Prepared as in example 43 using the product of example 17 step b)
MS (APCI) 401 (M+H⁺, 100%).

EXAMPLE 45

(+/-)-5-[[2,3-diftuorophenyl)methyl]thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

15 **[0217]** Prepared by the method of example 43 using the product of example 40 step e).
MP >250 °C
MS (APCI) 415 (M+H⁺, 100%).
NMR δH (*d*₆-DMSO) 7.39-7.04 (3H, m), 5.51 (1H, d), 4.68 (1H, t), 4.34 (2H, q), 4.22 (1H, m), 3.51-3.35 (4H, m), 3.32 (3H, s).

EXAMPLE 46

25 **7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt**

30 **[0218]** Prepared by the method of example 43 using the product from example 41 step d)
MP 231-2 °C
MS (APCI) 365 (M+H⁺, 100%).
NMR δH (*d*₆-DMSO) 7.41-7.18 (5H, m), 5.30 (1H, d), 4.63 (2H, s), 4.28 (2H, s), 4.06 (1H, m), 3.50 (4H, m).

EXAMPLE 47

7-[[[(1*R*)-2-Hydroxy-1-methylethyl]amino]-5-[[phenylmethyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

40 **[0219]** Prepared by the method of example 43 using the product of example 3 step d).
MP (shrinks 110) melts 221-225 °C
45 MS (APCI) 349 (M+H⁺ 100%).
NMR δH (*d*₆-DMSO) 7.41-7.18 (5H, m), 5.58 (1H, d), 4.65 (1H, t), 4.28 (2H, q), 4.11 (1H, m), 3.49-3.31 (2H, m), 1.08 (3H, d).

EXAMPLE 48

5-[[5-chloro-1,2,3-thiadiazol-4-yl]thio]-7-[[[(1*R*)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

55

(a) (2*R*)-2-[[2-amino-5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

[0220] Prepared by the method of example 32 step c), using the product of example 32 step b) and 5-chloro-4-(chloromethyl)-1,2,3-thiadiazole.

MS (APCI) 390 (M+H⁺, 100%).

(b) (2*R*)- 2-[[2-chloro-5-[(5-chloro-1,2,3-thiadiazol-4-yl)methyl]thio]thiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

[0221] Prepared by the method of example 40 step c) and using the product of example 48 step a)

MS (APCI) 409 (M+H⁺, 100%).

(c) (2*R*)-2-[[[(5-chloro-1,2,3-thiadiazol-4-yl)methyl]thio]-2-methoxythiazolo[4,5-*d*]pyrimidin-7-yl]amino]-1-propanol

[0222] Prepared by the method of example 1 step f) and using the product of example 48 step b)

MS (APCI) 405 (M+H⁺, 100%).

(d) 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thiol-7-[(1*R*)-2-hydroxy-1-methylethyl]amino]-thiazolo (4,5-*d*)pyrimidin-2(3*H*)-one.

[0223] Prepared by the method of example 1 step g) and using the product of example 48 step c)

MS (APCI) 391(M+H⁺, 100%).

[0224] NMR δH (*d*₆-DMSO) 12.39 (1H, s), 7.39 (1H, d), 4.76 (2H, AB), 4.70 (1H, t), 4.24 (1H, m), 3.48-3.30 (2H, m), 1.11 (3H, d)

Pharmacological Data

Ligand Binding Assay

[0225] [¹²⁵I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No. 85120602) (Lee et al. (1992) J. Biol. Chem. 267 pp 16293-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned into the eukaryotic expression vector RcCMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2% (w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH

7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease inhibitors (1mM phenyl methyl sulphonyl fluoride, 2μg/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5μg/ml leupeptin and 100μg/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH₂PO₄), 0.1 % (w/v) gelatin and 10% (v/v) glycerol. All assays were performed in a 96-well MultiScreen 0.45μm filtration plates (Millipore, U.K.). Each assay contained ~50pM [¹²⁵I]IL-8 and membranes (equivalent to ~200,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM CaCl₂, 1mM MgCl₂, 0.125mg/ml bacitracin and 0.1% (w/v) gelatin]. In addition, a compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to reach a final concentration of 1% (v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra γ-counter.

[0226] The compounds of formula (I) according to the Examples were found to have IC₅₀ values of less than (<) 10μM.

Intracellular Calcium Mobilisation Assay

[0227] Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly et al. (1997) Methods in Enzymology 287 pp70-72), in storage buffer [Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH₂PO₄) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

[0228] The chemokine GROα (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular free calcium were measured fluorometrically-by loading neutrophils with the calcium sensitive fluorescent dye, fluo-3, as described previously (Merritt et al. (1990) Biochem. J. 269, pp513-519). Cells were loaded for 1 hour at 37°C in loading buffer (storage buffer with 0.1% (w/v) gelatin) containing 5μM fluo-3 AM ester, washed with loading buffer and then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1% (w/v) bovine serum albumin (BSA), 1.8mM CaCl₂ and 1mM MgCl₂. The cells were pipetted into black walled, clear bottom, 96 well micro plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

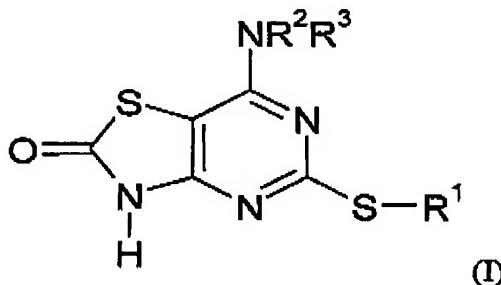
[0229] A compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to a final

concentration of 0.1% (v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of GRO α and the transient increase in fluo-3 fluorescence ($\lambda_{Ex} = 490\text{nm}$ and $\lambda_{Em} = 520\text{nm}$) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

[0230] The compounds of formula (I) according to the Examples were tested and found to be antagonists of the CXCR2 receptor in human neutrophils.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

R^1 represents a C_3 - C_7 carbocyclic, C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $NR^8SO_2R^9$, phenyl, naphthyl or a 5- or 6-membered aromatic ring containing one or more hetero atoms selected from N, S and O, the phenyl, naphthyl and aromatic rings being optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1 - C_6 alkyl or trifluoromethyl groups;

R^2 and R^3 each independently represent a hydrogen atom, or a C_3 - C_7 carbocyclic, C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

- (a) halogen atoms, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $NR^8SO_2R^9$

5 (b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁸ and itself optionally substituted by C₁-C₃-alkyl or halogen,

(c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR⁹, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl and trifluoromethyl groups;

10 R⁴ represents hydrogen, C₁-C₆ alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹¹ and -NR¹²R¹³

15 R⁵ and R⁶ independently represent a hydrogen atom or a C₁-C₆ alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹⁴ and -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶

20 or

25 R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, -OR¹⁴, -COOR¹⁴, -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶ or C₁-C₆ alkyl, itself optionally substituted by one or more substituents independently selected from halogen atoms and -NR¹⁵R¹⁶ and -OR¹⁷ groups;

30 R¹⁰ represents a hydrogen atom or a C₁-C₆-alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹⁷ and NR¹⁵R¹⁶; and

35 each of R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ independently represents a hydrogen atom or a C₁-C₆, alkyl, or a phenyl group

40 for use in the treatment of rheumatoid arthritis.

- 45 2. A compound according to claim 1, wherein R^1 represents an optionally substituted benzyl group for use in the treatment of rheumatoid arthritis.
- 50 3. A compound according to claim 1 or claim 2, wherein one of R^2 and R^3 is hydrogen and the other is C₁-C₆ alkyl substituted by hydroxy for use in the treatment of rheumatoid arthritis.

4. A compound according to claim 1 selected from:

7-[(2- Hydroxy- 1,1- dimethylethyl) amino]-
5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
2(3H)-one,
(R)- 7-[[1-(Hydroxymethyl) propyl] amino]-
5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
2(3H)-one,
(R)- 7-[(2- Hydroxy- 1- methylethyl) amino]-
5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
2(3H)-one,
5-[[2,3- Difluorophenyl) methyl] thio]- 7-[(2- hy-
droxy-1,1-dimethylethyl)amino] thiazolo[4,5-d]
pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl) methyl]thio]-7-[(1R)-2-
hydroxy-1-methylethyl]amino] thiazolo[4,5-d]
pyrimidin-2(3H)-one,
5-[[2,3- difluorophenyl) methyl] thio]- 7-[(2-hy-
droxyethoxy)ethyl]amino]thiazolo[4,5-d]pyrimi-
din-2(3H)-one,
5-[[2,3- difluorophenyl) methyl] thio]- 7-[[2- hy-
droxy-1-(hydroxymethyl)ethyl] amino] thiazolo
[4,5-d]pyrimidin-2(3H)-one,
7-[(2- aminoethyl) amino]- 5-[[2,3- difluorophenyl)
methyl] thio] thiazolo [4,5-d] pyrimidin- 2
(3H)-one,
5-[[2,3- difluorophenyl) methyl] thio]- 7-[(2- hy-
droxyethyl) amino] thiazolo [4,5-d] pyrimidin- 2
(3H)-one,
N-[2-[[5-[[2,3-difluorophenyl) methyl] thio]-2,3-
dihydro- 2- oxothiazolo [4,5-d] pyrimidin- 7- yl]
amino] ethyl]methanesulfonamide,
(+/-)- 5-[[2,3- difluorophenyl) methyl] thio)-
7-[[2-(2-hydroxyethoxy)- 1- methylethyl] amino]
thiazolo[4,5-d]pyrimidin-2(3H)-one,
7-[[1R)- 2- amino- 1- methylethyl] amino]-
5-[[2,3-difluorophenyl)methyl]thio] thiazolo
[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-difluorophenyl) methyl] thio]-7-[[[(1R)-2-
(2-hydroxyethyl) amino]- 1- methylethyl] amino]
thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-difluorophenyl) methyl] thio]-7-[[[(1R)-2-
(2-dimethylamino)-1-methylethyl]amino]thiazolo
[4,5-d]pyrimidin-2(3H)-one,
5-[[4-(2-aminoethoxy)- 3-chlorophenyl]methyl]
thio]-7-[[[(1R)-2- hydroxy- 1- methylethyl] amino]
thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[3- Chloro- 4- methoxyphenyl) methyl] thio]-
7-[[[(1R)-2- hydroxy- 1- methylethyl] amino] thia-
zolo[4,5-d]pyrimidin-2(3H)-one,
5-[[3- Chloro- 2- fluorophenyl) methyl] thio]-
7-[[[(1R)-2- hydroxy-1-methylethyl]amino] thia-
zolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3- Difluorophenyl) methyl] thio]- 7-[[[(3R,
4R)-4- hydroxypyrrolidin- 3- yl] amino]thiazolo
[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3- Difluorophenyl) methyl] thio]-
7-[(3R)-pyrrolidin-3-ylamino]thiazolo[4,5-d]py-

rimidin-2(3H)-one,
7-[(1R)- 2- Hydroxy- 1- methylethyl] amino]-
5-[[2-methyl-4-thiazoly) methyl]thio] thiazolo
[4,5-d]pyrimidin-2(3H)-one,
7-[[2-Hydroxy- 1-(hydroxymethyl) ethyl] amino]-
5-[[2-methyl-4-thiazoly) methyl] thio]thiazolo
[4,5-d]pyrimidin-2(3H)-one,
7-[(2-Hydroxy- 1,1-dimethylethyl)amino]-5-[[2-
methyl-4-thiazoly) methyl]thiol thiazolo[4,5-d]
pyrimidin-2(3H)-one,
7-[(2-Hydroxy-1,1-dimethylethyl)amino]-5-[[2-
methylphenyl)methyl]thio] thiazolo[4,5-d]pyri-
midin-2(3H)-one,
5-[(2-Furanyl)methyl]thio]-7-[[[(1R)-2-hydroxy-1-
methylethyl] amino] thiazolo [4,5-d] pyrimidin- 2
(3H)-one,
7-[[[(1R)-2-Amino- 1- methylethyl]amino]-5-[[3-
chloro-2-fluorophenyl)methyl]thio] thiazolo
[4,5-d]pyrimidin-2(3H)-one
(2S)- 2-[[5-[[2,3- Difluorophenyl) methyl] thio]-
2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]
amino]-3-hydroxy-propanamide,
7-[[[(1R)-2-hydroxy-1-methylethyl]amino]-5-[(2-
thienyl)methyl] thio] thiazolo [4,5-d] pyrimidin- 2
(3H)-one,
7-[[[(1R)-2-hydroxy-1-methylethyl]amino]-5[[3-
methyl- 4-(methylsulfonyl) phenyl] methyl] thio]
thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[3- chloro- 4- (trifluoromethoxy) phenyl] me-
thyl] thio]- 7-[[[(1R)- 2- hydroxy- 1- methylethyl]
amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2-fluoro- 3-(trifluoromethyl)phenyl]methyl]
thio]- 7-[[[(1R)- 2- hydroxy- 1- methylethyl] amino]
thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3- difluorophenyl) methyl] thio]-
7-[[2-(dimethylamino) ethyl] amino] thiazolo [4,
5-d]pyrimidin-2(3H)-one,
5-[[2-fluorophenyl) methyl] thio]-7-[[[(1R)-2-hy-
droxy-1-methylethyl]amino] thiazolo[4,5-d]pyri-
midin-2(3H)-one,
7-[[[(1R)- 2- hydroxy- 1- methylethyl] amino]-
5-[[2-methoxyphenyl)methyl]thio] thiazolo[4,5-d]
pyrimidin-2(3H)-one,
7-[[[(1R)-2-hydroxy-1-methylethyl]amino] thia-
zolo [4,5-d] pyrimidin- 2 (3H)-one,
7-[[[(1R)- 2- hydroxy- 1- methylethyl] amino]-
5-[[3-methylphenyl)methyl]thio] thiazolo[4,5-d]
pyrimidin-2(3H)-one,
5-[[2- fluoro- 3- methylphenyl) methyl] thio]-
7-[[[(1R)-2-hydroxy-1-methylethyl]amino] thia-
zolo [4,5-d] pyrimidin-2(3H)-one,
5-[[3-chlorophenyl) methyl]thio]-7-[[[(1R)-2-hy-
droxy-1-methylethyl]amino] thiazolo[4,5-d]pyri-
midin-2(3H)-one,
5-[[3-bromophenyl) methyl]thio]-7-[[[(1R)-2-hy-
droxy-1-methylethyl]amino] thiazolo[4,5-d]pyri-
midin-2(3H)-one,

5-[[[4-(difluoromethoxy) phenyl] methyl] thio]-7-[(1*R*)-2-hydroxy-1-methylethyl] amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 (+/-)-5-[[2,3-difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2-bromophenyl]methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2,3-Difluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-Chloro-2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 (+/-)-5-[[2,3-difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-Hydroxy-1-methylethyl] amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[5-chloro-1,2,3-thiadiazol-4-yl]thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

and their pharmaceutically acceptable salts and solvates for use in the treatment of rheumatoid arthritis.

5. A compound according to claim 1 selected from:

5-[[2,3-Difluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,
 5-[[3-Chloro-2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,
 (+/-)-5-[[2,3-difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,
 7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt, or
 7-[[1*R*]-2-Hydroxy-1-methylethyl] amino]-5-[(phenylmethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt

for use in the treatment of rheumatoid arthritis,

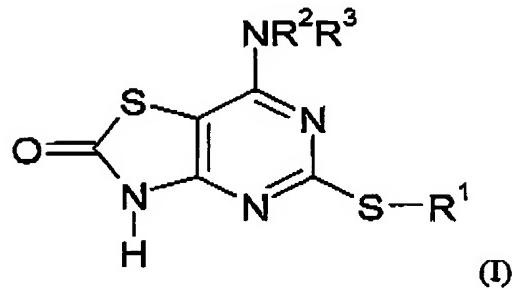
6. A compound according to claim 1 selected from:

7-[[1*R*]-2-amino-1-methylethyl] amino]-5-[(2,3-difluorophenyl)methyl] thio] thiazolo

[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,
 5-[(2,3-difluorophenyl) methyl] thio]-7-[[1*R*]-2-[(2-hydroxyethyl) amino]-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,
 5-[[2,3-difluorophenyl] methyl] thio]-7-[[1*R*]-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[4-(2-aminoethoxy)-3-chlorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one trifluoroacetate,
 5-[[2,3-difluorophenyl] methyl] thio]-7-[2-(dimethylamino)ethyl]amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one monohydrochloride, or
 5-[[2,3-Difluorophenyl] methyl] thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one dihydrochloride

for use in the treatment of rheumatoid arthritis.

7. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



in which

R¹ represents a C₃-C₇ carbocyclic, C₁-C₈ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl group, each of the groups being optionally substituted by one or more substituent groups independently selected from halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, phenyl, naphthyl or a 5- or 6-membered aromatic ring containing one or more hetero atoms selected from N, S and O, the phenyl, naphthyl and aromatic rings being optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl or trifluoromethyl groups;
 R² and R³ each independently represent a hydrogen atom, or a C₃-C₇ carbocyclic, C₁-C₈ alkyl

C_2 - C_6 alkenyl or C_2 - C_6 alkynyl group, the latter four groups may be optionally substituted by one or more substituent groups independently selected from:

- (a) halogen atoms, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹
- (b) a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁸ and itself optionally substituted by C₁-C₃-alkyl or halogen,
- (c) an aryl group or heteroaryl group each of which may be optionally substituted by one or more substituents independently selected from halogen atoms, cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR⁹, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆ alkyl and trifluoromethyl groups;

R⁴ represents hydrogen, C₁-C₆ alkyl or a phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹¹ and -NR¹²R¹³

R⁵ and R⁶ independently represent a hydrogen atom or a C₁-C₆ alkyl or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹⁴ and -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶

or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by one or more substituent groups independently selected from phenyl, -OR¹⁴, -COOR¹⁴, -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶ or C₁-C₆ alkyl, itself optionally substituted by one or more substituents independently selected from halogen atoms and -NR¹⁵R¹⁶ and -OR¹⁷ groups;

R¹⁰ represents a hydrogen atom or a C₁-C₆-alkyl or a phenyl group, the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, phenyl, -OR¹⁷ and -NR¹⁵R¹⁶; and each of R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ independently represents a hydrogen atom or a C₁-C₆, alkyl, or a phenyl group in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

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8. Use of a compound according to claim 1, wherein R¹ represents an optionally substituted benzyl group in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

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9. Use of a compound according to claim 1 or claim 2, wherein one of R² and R³ is hydrogen and the other is C₁-C₆ alkyl substituted by hydroxy in the manufacture of a medicament for use in rheumatoid arthritis.

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10. Use of a compound according to claim 1 selected from:

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7-[(2-Hydroxy-1,1-dimethyleethyl) amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
(R)-7-[[1-(Hydroxymethyl) propyl] amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
(R)-7-[(2-Hydroxy-1-methyleethyl) amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl] methyl] thio]-7-[(2-hydroxy-1,1-dimethyleethyl)amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl] methyl] thio]-7-[[1(R)-2-hydroxy-1-methyleethyl]amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl] methyl] thio]-7-[[2-(hydroxyethoxy)ethyl]amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
7-[(2-aminoethyl) amino]-5-[[2,3-Difluorophenyl] methyl] thio] thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl] methyl] thio]-7-[(2-hydroxyethyl) amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
N-[2-[[5-[[2,3-Difluorophenyl] methyl] thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]ethyl]methanesulfonamide,
(+/-)-5-[[2,3-Difluorophenyl] methyl] thio]-7-[[2-(2-hydroxyethoxy)-1-methyleethyl]amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
7-[[1(R)-2-amino-1-methyleethyl] amino]-5-[[2,3-Difluorophenyl] methyl] thio] thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[2,3-Difluorophenyl] methyl] thio]-7-[[1(R)-2-(dimethylamino)-1-methyleethyl]amino] thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[4-(2-aminoethoxy)-3-chlorophenyl] methyl] thio]-7-[[1(R)-2-hydroxy-1-methyleethyl] amino]

thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-Chloro- 4-methoxyphenyl] methyl] thio]-7-[[1*R*]-2-hydroxy- 1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-Chloro- 2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2,3-Difluorophenyl] methyl] thio]-7-[[3*R*, 4*R*]-4-hydroxypyrrolidin-3-yl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2,3-Difluorophenyl] methyl] thio]-7-[[3*R*]-pyrrolidin-3-ylamino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-Hydroxy- 1-methylethyl] amino]-5-[[2-methyl-4-thiazoly]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[2-Hydroxy-1-(hydroxymethyl) ethyl] amino]-5-[[2-methyl-4-thiazoly]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[2-Hydroxy-1,1-dimethylethyl] amino]-5-[[2-methylphenyl]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[2-Hydroxy-1,1-dimethylethyl] amino]-5-[[2-methylphenyl]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[(2-Furanyl methyl)thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-Amino- 1-methylethyl] amino]-5-[[3-chloro-2-fluorophenyl]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one
 (2*S*)-2-[[5-[[2,3-Difluorophenyl] methyl] thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl] amino]-3-hydroxy-propanamide,
 7-[[1*R*]-2-hydroxy-1-methylethyl] amino]-5-[(2-thienylmethyl) thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-hydroxy-1-methylethyl] amino]-5-[[3-methyl-4-(methylsulfonyl) phenyl] methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-chloro- 4-(trifluoromethoxy) phenyl] methyl] thio]-7-[[1*R*]-2-hydroxy- 1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2-fluoro- 3-(trifluoromethyl) phenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2,3-difluorophenyl] methyl] thio]-7-[[dimethylamino] ethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-hydroxy- 1-methylethyl] amino]-5-[[2-methoxyphenyl]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-hydroxy-1-methylethyl] amino]-5-[(2-phenoxyethyl) thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

7-[[1*R*]-2-hydroxy- 1-methylethyl] amino]-5-[[3-methylphenyl]methyl] thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-chlorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-bromophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[4-(difluoromethoxy) phenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 (+/-)-5-[[2,3-difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[2-hydroxy-1-(hydroxymethyl) ethyl] amino]-5-[(phenylmethyl)thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2-bromophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[2,3-Difluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[[3-Chloro- 2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 (+/-)-5-[[2,3-difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[2-hydroxy-1-(hydroxymethyl) ethyl] amino]-5-[(phenylmethyl)thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 7-[[1*R*]-2-Hydroxy- 1-methylethyl] amino]-5-[(phenylmethyl)thio] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

and their pharmaceutically acceptable salts and solvates, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

11. Use of a compound according to claim 1 selected from;

5-[[2,3-Difluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,
 5-[[3-Chloro- 2-fluorophenyl] methyl] thio]-7-[[1*R*]-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one sodium salt,
 (+/-)-5-[[2,3-difluorophenyl] methyl] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl] amino] thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

zolo[4,5-d]pyrimidin-2(3H)-one sodium salt,
7-[[2-hydroxy-1-(hydroxymethyl) ethyl] amino]-
5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
2(3H)-one sodium salt, or
7-[[*(1R)*-2-1-Hydroxy-1-methylethyl] amino]-
5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
2(3H)-one sodium salt

in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

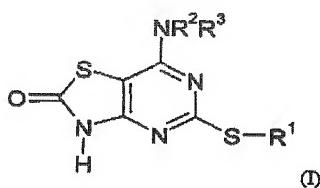
12. Use of a compound according to claim 1 selected from:

7-[[*(1R)*-2-amino-1-methylethyl] amino]-
5-[(2,3-difluorophenyl)methyl]thio] thiazolo[4,5-d]pyrimidin-2(3H)-one trifluoroacetate,
5-[(2,3-difluorophenyl) methyl] thio]-7-[[*(1R)*-2-(2-hydroxyethyl) amino]-1-methylethyl] amino]thiazolo[4,5-d]pyrimidin-2(3H)-one trifluoroacetate,
5-[(2,3-difluorophenyl) methyl] thio]-7-[[*(1R)*-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
5-[[4-(2-aminoethoxy)-3-chlorophenyl]methyl] thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl]amino] thiazolo[4,5-d]pyrimidin-2(3H)-one trifluoroacetate,
5-[(2,3-difluorophenyl) methyl] thio]-7-[2-(dimethylamino)ethyl] amino] thiazolo[4,5-d]pyrimidin-2(3H)-one monohydrochloride, or
5-[(2,3-Difluorophenyl) methyl] thio]-7-[*(3R)*-pyrrolidin-3-ylamino]thiazolo[4,5-d]pyrimidin-2(3H)-one dihydrochloride

in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

Patentansprüche

1. Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz oder Solvat davon:



worin

R¹ für eine C₃-C₇-carbocyclische, C₁-C₈-Alkyl-, C₂-C₆-Alkenyl- oder C₂-C₆-Alkinylgruppe steht,

die gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, Phenyl, Naphthyl oder einem 5- oder 6-gliedrigen aromatischen Ring mit einem oder mehreren, unter N, S und O ausgewählten Heteroatomen ausgewählte Substituentengruppen substituiert ist, wobei das Phenyl, das Naphthyl und die aromatischen Ringe gegebenenfalls durch einen oder mehrere, unabhängig voneinander unter Halogenatomen, Cyano-, Nitro-, -OR⁴-, -NR⁵R⁶-, -CONR⁵R⁶-, -COOR⁷-, -NR⁸COR⁹-, -SR¹⁰-, -SO₂R¹⁰-, -SO₂NR⁵R⁶-, -NR⁸SO₂R⁹-, C₁-C₆-Alkyl- und Trifluormethylgruppen ausgewählte Substituenten substituiert sind;

R² und R³ jeweils unabhängig voneinander für ein Wasserstoffatom oder für eine C₃-C₇-carbocyclische, C₁-C₈-Alkyl-, C₂-C₆-Alkenyl- oder C₂-C₆-Alkinylgruppe stehen, wobei die letztgenannten vier Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter:

- (a) Halogenatomen, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹,
- (b) einem 3- bis 8-gliedrigen Ring, der gegebenenfalls ein oder mehrere, unter O, S und NR⁸ ausgewählte Atome enthält und selbst gegebenenfalls durch C₁-C₃-Alkyl oder Halogen substituiert ist,
- (c) einer Aryl- oder Heterarylgruppe, die gegebenenfalls durch einen oder mehrere, unabhängig voneinander unter Halogenatomen, Cyano-, Nitro-, -OR⁴-, -NR⁵R⁶-, -CONR⁵R⁶-, -NR⁸COR⁹-, -SO₂NR⁵R⁶-, -NR⁸SO₂R⁹-, C₁-C₆-Alkyl- und Trifluormethylgruppen ausgewählte Substituenten substituiert sein kann,

ausgewählte Substituentengruppen substituiert sein können;

R⁴ für Wasserstoff, C₁-C₆-Alkyl oder eine Phenylgruppe steht, wobei die beiden letztgenannten Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, Phenyl, -OR¹¹ oder -NR¹²R¹³ ausgewählte Substituentengruppen substituiert sein können;

R⁵ und R⁶ unabhängig voneinander für ein Wasserstoffatom oder eine C₁-C₆-Alkyl- oder Phenylgruppe stehen, wobei die beiden letztgenannten Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, Phenyl, -OR¹⁴ und -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶ oder

$\text{NR}^{15}\text{SO}_2\text{R}^{16}$ ausgewählte Substituentengruppen substituiert sein können, oder R^5 und R^6 gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, ein 4- bis 7-gliedriges gesättigtes heterocyclisches Ringsystem bilden, welches gegebenenfalls ein weiteres, unter Sauerstoff- und Stickstoffatomen ausgewähltes Heteroatom enthält und gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Phenyl, - OR^{14} , - COOR^{14} , - $\text{NR}^{15}\text{R}^{16}$, - $\text{CONR}^{15}\text{R}^{16}$, - $\text{NR}^{15}\text{COR}^{16}$, - $\text{SONR}^{15}\text{R}^{16}$, - $\text{NR}^{15}\text{SO}_2\text{R}^{16}$ oder $\text{C}_1\text{-C}_6\text{-Alkyl}$, welches selbst gegebenenfalls durch einen oder mehrere, unabhängig voneinander unter Halogenatomen und - $\text{NR}^{15}\text{R}^{16}$ - und - OR^{17} -Gruppen ausgewählte Substituenten substituiert ist, ausgewählte Substituentengruppen substituiert sein kann; R^{10} für ein Wasserstoffatom oder eine $\text{C}_1\text{-C}_6\text{-Alkyl}$ - oder Phenylgruppe steht, wobei die beiden letztgenannten Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, Phenyl, - OR^{17} und - $\text{NR}^{15}\text{R}^{16}$ ausgewählte Substituentengruppen substituiert sein können; und R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} und R^{17} jeweils unabhängig voneinander für ein Wasserstoffatom oder eine $\text{C}_1\text{-C}_6\text{-Alkyl}$ - oder Phenylgruppe stehen,

zur Verwendung bei der Behandlung von rheumatoider Arthritis.

2. Verbindung nach Anspruch 1, worin R^1 für eine gegebenenfalls substituierte Benzylgruppe steht, zur Verwendung bei der Behandlung von rheumatoider Arthritis.

3. Verbindung nach Anspruch 1 oder 2, worin eine der Gruppen R^2 und R^3 für Wasserstoff und die andere für hydroxysubstituiertes $\text{C}_1\text{-C}_6\text{-Alkyl}$ steht, zur Verwendung bei der Behandlung von rheumatoider Arthritis.

4. Verbindung nach Anspruch 1, ausgewählt unter:

7-[(2-Hydroxy- 1,1-dimethylethyl) amino]-5-[(phenyl-methyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,

(*R*)- 7-[(1-Hydroxymethyl) propyl] amino]-5-[(phenyl-methyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,

(*R*)- 7-[(2-Hydroxy- 1- methylethyl) amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-d]pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(1R)-2-

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hydroxy- 1- methylethyl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxyethoxyethyl)amino]thiazolo[4,5-d]-pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxy-1-(hydroxymethyl)ethyl)amino]thiazolo[4,5-d]-pyrimidin-2(3H)-on,

7-[(2-Aminoethyl) amino]- 5-[(2,3-difluorphenyl)-methyl] thio] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxyethyl) amino] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,

N-[2-[(5-(2,3-Difluorphenyl) methyl)thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]-ethyl)methansulfonamid,

(+/-)- 5-[(2,3-Difluorphenyl) methyl] thio]-7-[(2-hydroxyethoxy)- 1- methylethyl] amino] thiazolo-[4,5-d]pyrimidin-2(3H)-on,

7-[(1*R*)- 2- Amino- 1- methylethyl] amino]-5-[(2,3-difluorphenyl) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl) methyl] thio]- 7-[(1*R*)-2-[(2-hydroxyethyl) amino]- 1- methylethyl] amino]-thiazolo[4,5-d]pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl) methyl] thio]- 7-[(1*R*)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-on,

5-[(4-(2-Aminoethoxy)- 3- chlorphenyl) methyl] thio]- 7-[(1*R*)-2-hydroxy- 1- methylethyl] amino] thiazolo-[4,5-d]pyrimidin-2(3H)-on,

5-[(3-Chlor- 4- methoxyphenyl) methyl] thio]- 7-[(1*R*)-2-hydroxy- 1- methylethyl] amino] thiazolo[4,5-d]-pyrimidin-2(3H)-on,

5-[(3-Chlor-2-fluorophenyl)methyl]thio]-7-[(1*R*)-2- hydroxy- 1- methylethyl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(3*R*,4*R*)-4-hydroxypyrrolidin- 3- yl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

5-[(2,3-Difluorphenyl)methyl]thio]-7-[(3*R*)-pyrrolidin- 3- yl] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,

7-[(1*R*)- 2- Hydroxy- 1- methylethyl] amino]-5-[(2-methyl- 4- thiazoly) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

7-[(2-Hydroxy- 1-(hydroxymethyl) ethyl] amino]-5-[(2-methyl- 4- thiazoly) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

7-[(2-Hydroxy- 1,1-dimethylethyl) amino]-5-[(2-methyl- 4- thiazoly) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,

7-[(2-Hydroxy- 1,1-dimethylethyl) amino]-5-[(2-methylphenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,

5-[(2-Furanyl)methyl]thio]-7-[(1*R*)-2-hydroxy- 1- methylethyl] amino] thiazolo [4,5-d] pyrimidin- 2

(3*H*)-on,
 7-[[*(1R)*-2-Amino-1-methylethyl]amino]-5-[[*(3-chlor- 2- fluorophenyl) methyl*] thio] thiazolo [4,5-d]-pyrimidin-2(*3H*)-on,
 (2*S*)-2-[[5-[[*(2,3-Difluorophenyl)methyl*]thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-*y*l]amino]-3-hydroxypropanamid,
 7-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-5-[(2-thienylmethyl) thio] thiazolo [4,5-d] pyrimidin-2 (*3H*)-on,
 7-[[*(1R)*- 2- Hydroxy- 1- methylethyl] amino]-5-[[*[3-methyl- 4- methylsulfonyl) phenyl] methyl*] thio]-thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 5-[[*[3- Chlor- 4- (trifluormethoxy) phenyl] methyl*]-thio]-7-[[*(1R)*- 2- hydroxy- 1- methylethyl] amino]-thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 5-[[*[2- Fluor- 3-(trifluormethyl) phenyl] methyl*]-thio]-7-[[*(1R)*- 2- hydroxy- 1- methylethyl] amino]-thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 5-[[*(2,3-Difluorophenyl) methyl*] thio]-7-[2-[(dime-
 thylamino) ethyl] amino] thiazolo [4,5-d]-pyrimidin-2(*3H*)-on,
 5-[[*(2- Fluorophenyl) methyl*] thio]-7-[[*(1R)*- 2- hydroxy-1-methylethyl]amino]thiazolo[4,5-d]-pyri-
 midin-2(*3H*)-on,
 7-[[*(1R)*- 2- Hydroxy- 1- methylethyl] amino]-5-[[*(2-methoxyphenyl)methyl*]thio]thiazolo[4,5-d]-pyrimidin-2(*3H*)-on,
 7-[[*(1R)*-2-Hydroxy-1-methylethyl]amino]-5-[(2-phenoxyethyl) thio] thiazolo [4,5-d] pyrimidin- 2 (*3H*)-on,
 7-[[*(1R)*- 2- Hydroxy- 1- methylethyl] amino]-5-[[*(3-methylphenyl)methyl*]thio]thiazolo[4,5-d]-pyrimidin-2(*3H*)-on,
 5-[[*(2- Fluor- 3- methylphenyl) methyl*] thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-d]-pyrimidin-2(*3H*)-on,
 5-[[*(3-Chlorphenyl) methyl*] thio]-7-[[*(1R)*-2- hydroxy-1-methylethyl]amino]thiazolo[4,5-d]-pyri-
 midin-2(*3H*)-on,
 5-[[*(3-Bromphenyl) methyl*] thio]-7-[[*(1R)*-2- hydroxy-1-methylethyl]amino]thiazolo[4,5-d]pyri-
 midin-2(*3H*)-on,
 5-[[*(4-Difluormethoxy) phenyl*] methyl] thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl] amino] thiazolo[4,5-d]-pyrimidin-2(*3H*)-on,
 (+/-)-5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 7-[[*[2-Hydroxy-1-(hydroxymethyl)ethyl] amino*]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 5-[[*(2-Bromphenyl) methyl*] thio]-7-[[*(1R)*-2- hydroxy-1-methylethyl]amino]thiazolo[4,5-d]pyri-
 midin-2(*3H*)-on,
 5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[*(1R)*-2- hydroxy- 1- methylethyl] amino] thiazolo [4,5-d]-pyrimidin-2(*3H*)-on,

5-[[*(3- Chlor- 2- fluorophenyl) methyl*] thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl] amino]thiazolo[4,5-d]-pyrimidin-2(*3H*)-on,
 (+/-)-5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 7-[[*[2-Hydroxy-1-(hydroxymethyl)ethyl] amino*]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 7-[[*(1R)*- 2- Hydroxy- 1- methylethyl] amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 5-[(5-Chlor-1,2,3-thiadiazol-4-*y*)thio]-7-[[*(1R)*- 2- hydroxy- 1- methylethyl] amino] thiazolo [4,5-d]-pyrimidin-2(*3H*)-on,

und pharmazeutisch annehmbare Salze und Solvate davon zur Verwendung bei der Behandlung von rheumatoider Arthritis.

5. Verbindung nach Anspruch 1, ausgewählt unter:

5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[*(1R)*-2- hydroxy- 1- methylethyl] amino]-thiazolo [4,5-d]-pyrimidin-2(*3H*)-on-Natriumsalz,
 5-[[*(3- Chlor- 2- fluorophenyl) methyl*] thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl] amino]thiazolo[4,5-d]-pyrimidin-2(*3H*)-on-Natriumsalz,
 (+/-)-5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[2-hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(*3H*)-on-Natriumsalz,
 7-[[*[2-Hydroxy-1-(hydroxymethyl)ethyl] amino*]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(*3H*)-on-Natriumsalz oder
 7-[[*(1R)*- 2- Hydroxy- 1- methylethyl] amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(*3H*)-on-Natriumsalz,

zur Verwendung bei der Behandlung von rheumatoider Arthritis.

6. Verbindung nach Anspruch 1, ausgewählt unter:

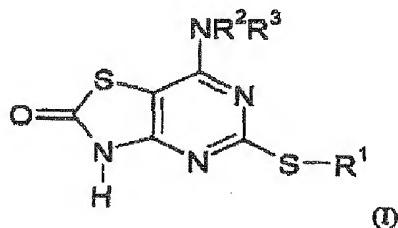
7-[[*(1R)*- 2- Amino- 1- methylethyl] amino]-5-[[*(2,3-Difluorophenyl)methyl*] thio]thiazolo[4,5-d]-pyrimidin-2(*3H*)-on-trifluoracetat,
 5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[*(1R)*-2-[(2-hydroxyethyl) amino]-1-methylethyl] amino]thiazolo[4,5-d]pyrimidin-2(*3H*)-on-trifluoracetat,
 5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[*(1R)*-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(*3H*)-on,
 5-[[*(4-(2-Aminoethoxy)-3-chlorophenyl)methyl*] thio]-7-[[*(1R)*-2-hydroxy-1-methylethyl] amino]thiazolo[4,5-d]pyrimidin-2 (*3H*)-on-trifluoracetat,
 5-[[*(2,3-Difluorophenyl)methyl*] thio]-7-[[2-[(dime-

thylamino) ethyl] amino] thiazolo [4,5-*d*]-pyrimidin-2(3H)-on-monohydrochlorid oder 5-[[2,3-Difluorphenyl)methyl]thio]-7-[(3*R*)-pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-on-dihydrochlorid,

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zur Verwendung bei der Behandlung von rheumatoide Arthritis.

7. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes oder Solvats davon:



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worin

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R¹ für eine C₃-C₇-carbocyclische, C₁-C₈-Alkyl-, C₂-C₆-Alkenyl- oder C₂-C₆-Alkinylgruppe steht, die gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, Phenyl, Naphthyl oder einem 5- oder 6-gliedrigen aromatischen Ring mit einem oder mehreren, unter N, S und O ausgewählten Heteroatomen ausgewählte Substituentengruppen substituiert ist, wobei das Phenyl, das Naphthyl und die aromatischen Ringe gegebenenfalls durch einen oder mehrere, unabhängig voneinander unter Halogenatomen, Cyano-, Nitro-, -OR⁴-, -NR⁵R⁶-, -CONR⁵R⁶-, -COOR⁷-, -NR⁸COR⁹-, -SR¹⁰-, -SO₂R¹⁰-, -SO₂NR⁵R⁶-, -NR⁸SO₂R⁹-, C₁-C₆-Alkyl- und Trifluormethylgruppen ausgewählte Substituenten substituiert sind;

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R² und R³ jeweils unabhängig voneinander für ein Wasserstoffatom oder für eine C₃-C₇-carbocyclische, C₁-C₈-Alkyl-, C₂-C₆-Alkenyl- oder C₂-C₆-Alkinylgruppe stehen, wobei die letztgenannten vier Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter:

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(a) Halogenatomen, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹,

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(b) einem 3- bis 8-gliedrigen Ring, der gegebenenfalls ein oder mehrere, unter O, S und NR⁸ ausgewählte Atome enthält und

selbst gegebenenfalls durch C₁-C₃-Alkyl oder Halogen substituiert ist,

(c) einer Aryl- oder Heteroarylgruppe, die gegebenenfalls durch einen oder mehrere, unabhängig voneinander unter Halogenatomen, Cyano-, Nitro-, -OR⁴-, -NR⁵R⁶-, -CONR⁵R⁶-, -NR⁸COR⁹-, -SO₂NR⁵R⁶-, -NR⁸SO₂R⁹-, C₁-C₆-Alkyl- und Trifluormethylgruppen ausgewählte Substituenten substituiert sein kann,

ausgewählte Substituentengruppen substituiert sein können;

R⁴ für Wasserstoff, C₁-C₆-Alkyl oder eine Phenylgruppe steht, wobei die beiden letztgenannten Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, Phenyl, -OR¹¹ oder -NR¹²R¹³ ausgewählte Substituentengruppen substituiert sein können;

R⁵ und R⁶ unabhängig voneinander für ein Wasserstoffatom oder eine C₁-C₆-Alkyl- oder Phenylgruppe stehen, wobei die beiden letztgenannten Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, Phenyl, -OR¹⁴ und -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶ oder NR¹⁵SO₂R¹⁶ ausgewählte Substituentengruppen substituiert sein können, oder

R⁵ und R⁶ gemeinsam mit dem Stickstoffatom, an das sie gebunden sind, ein 4- bis 7-gliedriges gesättigtes heterocyclisches Ringsystem bilden, welches gegebenenfalls ein weiteres, unter Sauerstoff- und Stickstoffatomen ausgewähltes Heteroatom enthält und gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Phenyl, -OR¹⁴, -COOR¹⁴, -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, -NR¹⁵SO₂R¹⁶ oder C₁-C₆-Alkyl, welches selbst gegebenenfalls durch einen oder mehrere, unabhängig voneinander unter Halogenatomen und -NR¹⁵R¹⁶- und -OR¹⁷-Gruppen ausgewählte Substituenten substituiert ist, ausgewählte Substituentengruppen substituiert sein kann;

R¹⁰ für ein Wasserstoffatom oder eine C₁-C₆-Alkyl- oder Phenylgruppe steht, wobei die beiden letztgenannten Gruppen gegebenenfalls durch eine oder mehrere, unabhängig voneinander unter Halogenatomen, Phenyl, -OR¹⁷ und -NR¹⁵R¹⁶ ausgewählte Substituentengruppen substituiert sein können; und

R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ und R¹⁷ jeweils unabhängig voneinander für ein Wasserstoffatom oder eine C₁-C₆-Alkyl- oder Phenylgruppe stehen,

bei der Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von rheumatoide Arthritis.

8. Verwendung einer Verbindung nach Anspruch 1, worin R¹ für eine gegebenenfalls substituierte Benzylgruppe steht, bei der Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von rheumatoider Arthritis.
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9. Verwendung einer Verbindung nach Anspruch 1 oder 2, worin eine der Gruppen R² und R³ für Wasserstoff und die andere für hydroxysubstituiertes C₁-C₆-Alkyl steht, bei der Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von rheumatoider Arthritis.
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10. Verwendung einer Verbindung nach Anspruch 1, ausgewählt unter:
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- 7-[2- Hydroxy- 1,1- dimethylethyl] amino]-5-[(phenyl-methyl) thio] thiazolo [4, 5-d] pyrimidin-2 (3H)-on,
- (R)- 7-[[1-(Hydroxymethyl) propyl] amino]-5-[(phenyl-methyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- (R)- 7-[(2-(Hydroxy- 1- methylethyl) amino]-5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxy-1,1-dimethylethyl)amino]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[(2,3-Difluorphenyl)methyl]thio]-7-[(1R)-2-hydroxy- 1- methylethyl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- 5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxyethoxy)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 7-[(2- Aminoethyl) amino]- 5-[(2,3- difluorphenyl)-methyl] thio] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,
- 5-[(2,3-Difluorphenyl)methyl]thio]-7-[(2-hydroxyethyl) amino] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,
- N-[2-[[5-(2,3-Difluorphenyl) methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]-ethyl]methansulfonamid,
- (+/-)- 5-[(2,3- Difluorphenyl) methyl] thio]-7-[[2-(2-hydroxyethoxy)- 1- methylethyl] amino] thiazolo-[4,5-d]pyrimidin-2(3H)-on,
- 7-[(1R)- 2- Amino- 1- methylethyl] amino]-5-[(2,3-difluorphenyl) methyl]thio]thiazolo[4,5-d]-pyrimidin-2(3H)-on,
- 5-[(2,3- Difluorphenyl) methyl] thio]- 7-[(1R)-2-[(2-hydroxyethyl) amino]- 1- methylethyl] amino]-thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[(2,3- Difluorphenyl) methyl] thio]- 7-[(1R)-2-(dimethylamino)-1-methylethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 55
- 5-[[4-(2- Aminoethoxy)- 3- chlorphenyl] methyl] thio]- 7-[[1(R)-2-hydroxy- 1- methylethyl] amino] thiazolo-[4,5-d]pyrimidin-2(3H)-on,
- 5-[[3- Chlor- 4- methoxyphenyl] methyl] thio]- 7-[[1(R)-2-hydroxy- 1- methylethyl] amino] thiazolo[4,5-d]-pyrimidin-2(3H)-on,
- 5-[[3-Chlor-2-fluorophenyl)methyl]thio]-7-[[1(R)-2- hydroxy- 1- methylethyl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- 5-[[2,3-Difluorphenyl)methyl]thio]-7-[(3R,4R)-4-hydroxypyrrolidin- 3- yl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- 5-[[2,3-Difluorphenyl)methyl]thio]-7-[(3R)-pyrrolidin- 3- ylamino] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,
- 7-[[1(R)- 2- Hydroxy- 1- methylethyl] amino]-5-[(2-methyl- 4- thiazolyl) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- 7-[[2-Hydroxy- 1-(hydroxymethyl) ethyl] amino]-5-[(2-methyl- 4- thiazolyl) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- 7-[(2-Hydroxy-1,1-dimethylethyl) amino]-5-[(2-methylphenyl)methyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[(2-Furanyl methyl)thio]-7-[[1(R)-2-hydroxy-1-methylethyl] amino] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,
- 7-[[1(R)-2-Amino-1-methylethyl] amino]-5-[[3-chlor- 2- fluorophenyl) methyl] thio] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- (2S)-2-[[5-[(2,3-Difluorphenyl)methyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]-3-hydroxypropanamid,
- 7-[[1(R)-2-Hydroxy-1-methylethyl]amino]-5-[(2-thienylmethyl) thio] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,
- 7-[[1(R)- 2- Hydroxy- 1- methylethyl] amino]-5-[[3-methyl- 4- methylsulfonyl) phenyl] methyl] thio]-thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[[3- Chlor- 4-(trifluormethoxy) phenyl] methyl]-thio]- 7-[(1R)- 2- hydroxy- 1- methylethyl] amino]-thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[[2- Fluor- 3-(trifluormethyl) phenyl] methyl]-thio]- 7-[(1R)- 2- hydroxy- 1- methylethyl] amino]-thiazolo[4,5-d]pyrimidin-2(3H)-on,
- 5-[[2,3-Difluorphenyl)methyl]thio]-7-[2-[(dimethylamino) ethyl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-on,
- 5-[(2- Fluorphenyl) methyl] thio]- 7-[[1(R)-2-hydroxy-1-methylethyl]amino]thiazolo[4,5-d]-pyrimidin-2(3H)-on,
- 7-[[1R)- 2- Hydroxy- 1- methylethyl] amino]-5-[(2-methoxyphenyl)methyl]thio]thiazolo[4,5-d]-pyrimidin-2(3H)-on,
- 7-[[1(R)-2-Hydroxy-1-methylethyl]amino]-5-[(2-

phenoxyethyl) thio] thiazolo [4,5-d] pyrimidin- 2 (3H)-on,
 7-[(1R)- 2- Hydroxy- 1- methylethyl] amino]-
 5-[(3-methylphenyl)methyl]thio]thiazolo[4,5-d]
 pyrimidin-2(3H)-on,
 5-[(2- Fluor- 3- methylphenyl) methyl] thio]-
 7-[(1R)-2-hydroxy- 1- methylethyl] amino] thia-
 zolo[4,5-d]pyrimidin-2(3H)-on,
 5-[(3-Chlorphenyl) methyl]thio]- 7-[(1R)-2-hy-
 droxy-1-methylethyl]amino]thiazolo[4,5-d]pyri-
 midin-2(3H)-on,
 5-[(3-Bromphenyl) methyl]thio]- 7-[(1R)-2-hy-
 droxy-1-methylethyl]amino]thiazolo[4,5-d]pyri-
 midin-2(3H)-on,
 5-[[4-(Difluormethoxy) phenyl] methyl] thio]-
 7-[(1R)-2-hydroxy- 1- methylethyl] amino] thia-
 zolo[4,5-d]pyrimidin-2(3H)-on,
 (+/-)- 5-[(2,3- Difluorophenyl) methyl] thio]- 7-[[2-
 hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo-
 [4,5-d]pyrimidin-2(3H)-on,
 7-[[2-Hydroxy-1-(hydroxymethyl) ethyl] amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
 2(3H)-on,
 5-[(2-Bromphenyl) methyl]thio]- 7-[(1R)-2-hy-
 droxy-1-methylethyl]amino]thiazolo[4,5-d]pyri-
 midin-2(3H)-on,
 5-[(2,3- Difluorophenyl) methyl]thio]- 7-[(1R)-2-
 hydroxy- 1- methylethyl] amino] thiazolo
 [4,5-d]-pyrimidin-2(3H)-on,
 5-[(3- Chlor- 2- fluorophenyl) methyl] thio]-
 7-[(1R)-2-hydroxy- 1- methylethyl] amino] thia-
 zolo[4,5-d]pyrimidin-2(3H)-on,
 (+/-)- 5-[(2,3- Difluorophenyl) methyl] thio]- 7-[[2-
 hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo-
 [4,5-d]pyrimidin-2(3H)-on,
 7-[[2-Hydroxy-1-(hydroxymethyl) ethyl] amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
 2(3H)-on,
 7-[(1R)- 2- Hydroxy- 1- methylethyl] amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
 2(3H)-on,
 5-[(5-Chlor-1,2,3-thiadiazol-4-yl)thio]- 7-[(1R)-
 2-hydroxy- 1- methylethyl] amino] thiazolo [4,5-
 d]pyrimidin-2(3H)-on,

und pharmazeutisch annehmbaren Salzen und Sol-
 vaten davon bei der Herstellung eines Arzneimittels
 zur Verwendung bei der Behandlung von rheumato-
 ider Arthritis.

11. Verwendung einer Verbindung nach Anspruch 1,
 ausgewählt unter:

5-[(2,3- Difluorophenyl) methyl] thio]- 7-[(1R)-2-
 hydroxy- 1- methylethyl] amino]-thiazolo [4,5-
 d]pyrimidin-2(3H)-on-Natriumsalz,
 5-[(3- Chlor- 2- fluorophenyl) methyl] thio]-
 7-[(1R)-2-hydroxy- 1- methylethyl] amino] thia-

zolo[4,5-d]-pyrimidin-2(3H)-on-Natriumsalz,
 (+/-)- 5-[(2,3- Difluorophenyl) methyl] thio]- 7-[[2-
 hydroxy-1-(methoxymethyl)ethyl]amino]thiazolo-
 [4,5-d]pyrimidin-2(3H)-on-Natriumsalz,
 7-[[2-Hydroxy-1-(hydroxymethyl) ethyl] amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
 2(3H)-on-Natriumsalz oder
 7-[(1R)- 2- Hydroxy- 1- methylethyl] amino]-
 5-[(phenylmethyl)thio]thiazolo[4,5-d]pyrimidin-
 2(3H)-on-Natriumsalz,

bei der Herstellung eines Arzneimittels zur Verwen-
 dung bei der Behandlung von rheumatoider Arthritis.

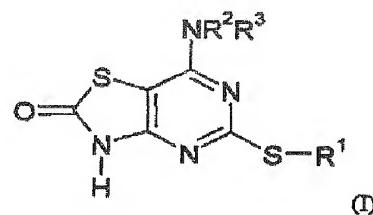
12. Verwendung einer Verbindung nach Anspruch 1,
 ausgewählt unter:

7-[(1R)- 2- Amino- 1- methylethyl] amino]-
 5-[(2,3- difluorophenyl) methyl] thio] thiazolo
 [4,5-d]-pyrimidin-2(3H)-on-trifluoracetat,
 5-[(2,3- Difluorophenyl) methyl] thio]- 7-[(1R)-
 2-[(2-hydroxyethyl) amino]- 1- methylethyl] ami-
 no]-thiazolo[4,5-d]pyrimidin-2(3H)-on-trifluora-
 cetat,
 5-[(2,3- Difluorophenyl) methyl] thio]- 7-[(1R)-
 2-(dimethylamino)-1-methylethyl]amino]thiazolo-
 [4,5-d]pyrimidin-2(3H)-on,
 5-[[4-(2- Aminoethoxy)-3- chlorphenyl] methyl]
 thio]- 7-[(1R)-2-hydroxy- 1- methylethyl] amino]-
 thiazolo-[4,5-d] pyrimidin- 2 (3H)-on-trifluorace-
 tat,
 5-[(2,3- Difluorophenyl) methyl] thio]- 7-[2-[(di-
 methylamino) ethyl] amino] thiazolo [4,5- d]-pyrimi-
 din-2(3H)-on-monohydrochlorid oder 5-[(2,3-
 Difluorophenyl)methyl]thio]-7-[(3R)-pyrrolidin-3-
 ylamino]thiazolo[4,5-d]pyrimidin-2(3H)-on-di-
 hydrochlorid,

bei der Herstellung eines Arzneimittels zur Verwen-
 dung bei der Behandlung von rheumatoider Arthritis.

Revendications

1. Composé de formule (I) ou sel ou solvate pharma-
 ceutiquement acceptable de celui-ci :



dans laquelle :

R¹ représente un groupement C₃-C₇ carbocyclique, C₁-C₈-alkyle, C₂-C₆-alcényle ou C₂-C₆-alcynyle, chacun des groupements étant éventuellement substitué par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d' halogène, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, phényle, naphtyle ou un cycle aromatique ayant 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi N, S et O, les cycles phényle, naphtyle et aromatiques étant éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les atomes d'halogène, les groupements cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆-alkyle ou trifluorométhyle ; R² et R³ représentent, chacun indépendamment, un atome d'hydrogène ou un groupement C₃-C₇ carbocyclique, C₁-C₈-alkyle, C₂-C₆-alcényle ou C₂-C₆-alcynyle, ces quatre groupements pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi :

- (a) les atomes d'halogène, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹,
- (b) un cycle ayant 3 à 8 chaînons contenant éventuellement un ou plusieurs atomes choisis parmi O, S, NR⁸ et étant lui-même éventuellement substitué par C₁-C₃-alkyle ou halogène,
- (c) un groupement aryle ou un groupement hétéroaryle, chacun pouvant être éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les atomes d'halogène, les groupements cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR⁹, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆-alkyle et trifluorométhyle,

R⁴ représente hydrogène, un groupement C₁-C₆-alkyle ou phényle, ces deux derniers pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, phényle, -OR¹¹ et -NR¹²R¹³ ;

R⁵ et R⁶ représentent indépendamment un atome d'hydrogène ou un groupement C₁-C₆-alkyle ou phényle, ces deux derniers pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, phényle, -OR¹⁴ et -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶, ou

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R⁵ et R⁶ forment, conjointement avec l'atome d'azote auquel ils sont liés, un système de cycles hétérocyclique saturé ayant 4 à 7 chaînons contenant éventuellement un hétéroatome supplémentaire choisi parmi les atomes d'oxygène et d'azote, ce système de cycles pouvant être éventuellement substitué par un ou plusieurs groupements substituants choisis indépendamment parmi phényle, -OR¹⁴, -COOR¹⁴, -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, -NR¹⁵SO₂R¹⁶ ou C₁-C₆-alkyle, lui-même étant éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les atomes d'halogène et les groupements -NR¹⁵R¹⁶ et -OR¹⁷ ;

R¹⁰ représente un atome d'hydrogène ou un groupement C₁-C₆-alkyle ou phényle, ces deux derniers pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, phényle, -OR¹⁷ et -NR¹⁵R¹⁶ ; et

chacun de R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ représente indépendamment un atome d'hydrogène ou un groupement C₁-C₆-alkyle ou phényle,

destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

2. Composé selon la revendication 1, **caractérisé en ce que** R¹ représente un groupement benzyle éventuellement substitué, destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

3. Composé selon la revendication 1 ou la revendication 2, **caractérisé en ce que** l'un de R² et R³ est hydrogène et l'autre est C₁-C₆-alkyle substitué par hydroxy, destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

4. Composé selon la revendication 1, choisi parmi :

la 7-[(2-hydroxy-1,1-diméthyléthyl)amino]-5-[(phénylméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,

la (R)-7-[[1-(hydroxyméthyl)propyl]amino]-5-[(phénylméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,

la (R)-7-[(2-hydroxy-1-méthyléthyl)amino]-5-[(phénylméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,

la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hydroxy-1,1-diméthyléthyl)amino] thiazolo [4,5-d]-pyrimidin-2(3H)-one,

la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1R)-2-hydroxy-1-méthyléthyl] amino] thiazolo [4,5-d]-pyrimidin-2(3H)-one,

la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hy-

droxyéthoxy) éthyl] amino] thiazolo [4,5- d]-pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[[2-hydroxy- 1-(hydroxyméthyl) éthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3H)-one,
la 7-[(2-aminoéthyl)amino]-5-[(2,3-difluorophényl) méthyl] thio] thiazolo [4,5-*d*] pyrimidin- 2 (3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hydroxyéthyl) amino] thiazolo [4,5-*d*] pyrimidin- 2 (3H)-one,
le *N*-[2-[[5-[(2,3-difluorophényl)méthyl]thio]-2, 3-dihydro- 2- oxothiazolo [4,5-*d*] pyrimidin- 7- yl]-amino]éthyl]méthanesulfonamide,
la (+/-)-5-[(2,3-difluorophényl)méthyl]thio]-7- [[2-(2- hydroxyéthoxy)- 1- méthyléthyl] amino]-thiazolo[4,5-*d*]pyrimidin-2(3H)-one,
la 7-[(1*R*)-2-amino-1-méthyléthyl]amino]-5- [[(2,3- difluorophényl) méthyl] thio] thiazolo [4, 5-*d*]-pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1*R*)- 2-[(2- hydroxyéthyl) amino]- 1- méthyléthyl] amino]-thiazolo[4,5-*d*]pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1*R*)- 2-(diméthylamino)-1-méthyléthyl]amino]thiazolo-[4,5-*d*]pyrimidin-2(3H)-one,
la 5-[[4-(2-aminoéthoxy)-3-chlorophényl)méthyl]-thio]- 7-[(1*R*)- 2- hydroxy- 1- méthyléthyl] amino]-thiazolo[4,5-*d*]pyrimidin-2(3H)-one,
la 5-[[3-chloro-4-méthoxyphényl)méthyl]thio]-7- [[(1*R*)- 2- hydroxy- 1- méthyléthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3H)-one,
la 5-[[3-chloro-2-fluorophényl)méthyl]thio]-7- [[(1*R*)- 2- hydroxy- 1- méthyléthyl] amino] thiazolo-[4, 5-*d*]pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(3*R*, 4*R*)-4- hydroxypyrrolidin- 3- yl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(3*R*)- pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2 (3H)-one,
la 7-[(1*R*)-2-hydroxy-1-méthyléthyl]amino]-5- [[(2- méthyl- 4- thiazoly) méthyl] thio] thiazolo [4,5-*d*]-pyrimidin-2(3H)-one,
la 7-[[2-hydroxy-1-(hydroxyméthyl)éthyl]amino]-5- [[(2-méthyl-4-thiazoly)méthyl]thio]thiazolo-[4,5-*d*]pyrimidin-2(3H)-one,
la 7-[(2-hydroxy-1,1-diméthyléthyl)amino]-5- [[(2- méthyl- 4- thiazoly) méthyl] thio] thiazolo [4,5-*d*]-pyrimidin-2(3H)-one,
la 7-[(2-hydroxy-1,1-diméthyléthyl)amino]-5- [[(2- méthylphényl) méthyl] thio] thiazolo [4,5-*d*] pyrimidin-2(3H)-one,
la 5-[(2-furanyl)méthyl]thio]-7-[(1*R*)-2-hydroxy- 1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2 (3H)-one,
la 7-[(1*R*)-2-amino-1-méthyléthyl]amino]-5- [[(3-chloro-2-fluorophényl) méthyl]thio]thiazolo

[4,5-*d*]-pyrimidin-2(3*H*)-one,
la (2*S*)-2-[[5-[(2,3-difluorophényl)méthyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-*d*]pyrimidin-7-yl]-amino]-3-hydroxypropanamide,
la 7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]-5-[[2-thiénylméthyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]-5-[[3-méthyl-4-(methylsulfonyl)phényle]méthyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[3-chloro-4-(trifluorométhoxy)phényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2-fluoro-3-(trifluorométhyl)phényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2,3-difluorophényle]méthyl]thio]-7-[2-[(diméthylamino)éthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2-fluorophényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]-5-[[2-méthoxyphényle]méthyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]-5-[[2-phénoxyéthyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]-5-[[3-méthylphényle]méthyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2-fluoro-3-méthylphényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[3-chlorophényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[3-bromophényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[4-(difluorométhoxy)phényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la (+/-)-5-[[2,3-difluorophényle]méthyl]thio]-7-[[2-hydroxy-1-(méthoxyméthyl)éthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[2-hydroxy-1-(hydroxyméthyl)éthyl]amino]-5-[[phényleméthyl]thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2-bromophényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2,3-difluorophényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[3-chloro-2-fluorophényle]méthyl]thio]-7-[[*(1R*)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,

la (+/-)-5-[(2,3-difluorophényl)méthyl]thio]-7-
[[2-hydroxy-1-(méthoxyméthyl) éthyl] amino]
thiazolo-[4,5-d]pyrimidin-2(3H)-one,
la 7-[[2-hydroxy-1-(hydroxyméthyl) éthyl]amino]-5-[(phényleméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
la 7-[[1R)-2-hydroxy-1-méthyléthyl]amino]-5-
[(phényleméthyl)thio]thiazolo[4,5-d]pyrimidin-2
(3H)-one,
la 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-
[[1R)-2-hydroxy-1-méthyléthyl]amino]thiazolo-[4,5-d]pyrimidin-2(3H)-one,

et leurs sels et solvates pharmaceutiquement acceptables, destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

5. Composé selon la revendication 1, choisi parmi :

le sel sodique de 5-[(2,3-difluorophényl)méthyl]-thio]-7-[[1R)-2-hydroxy-1-méthyléthyl]amino]-thiazolo[4,5-d]pyrimidin-2(3H)-one,
le sel sodique de 5-[(3-chloro-2-fluorophényl)méthyl]thio]-7-[[1R)-2-hydroxy-1-méthyléthyl]-amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
le sel sodique de (+/-)-5-[(2,3-difluorophényl)méthyl]thio]-7-[[2-hydroxy-1-(méthoxyméthyl)-éthyl] amino] thiazolo [4,5-d] pyrimidin- 2 (3H)-one,
le sel sodique de 7-[[2-hydroxy-1-(hydroxyméthyl)-éthyl]amino]-5-[(phényleméthyl)thio]thiazolo-[4,5-d]pyrimidin-2(3H)-one, ou
le sel sodique de 7-[[1R)-2-hydroxy-1-méthyléthyl] amino]-5-[(phényleméthyl) thio] thiazolo-[4,5-d]pyrimidin-2(3H)-one,

destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

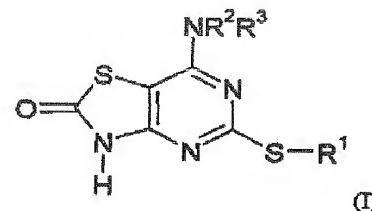
6. Composé selon la revendication 1, choisi parmi :

le trifluoroacétate de 7-[[1R)-2-amino-1-méthyl-éthyl] amino]-5-[(2,3-difluorophényl) méthyl]thio]-thiazolo[4,5-d]pyrimidin-2(3H)-one,
le trifluoroacétate de 5-[(2,3-difluorophényl)méthyl]thio]-7-[[1R)-2-[(2-hydroxyéthyl) amino]-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[[1R)-2-(diméthylamino)-1-méthyléthyl]amino]thiazolo-[4,5-d]pyrimidin-2(3H)-one,
le trifluoroacétate de 5-[[4-(2-aminoéthoxy)-3-chlorophényl] méthyl]thio]-7-[[1R)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
le monochlorhydrate de 5-[(2,3-difluorophényl)méthyl] thio]-7-[2-(diméthylamino) éthyl]amino]-thiazolo[4,5-d]pyrimidin-2(3H)-one, ou

le dichlorhydrate de 5-[(2,3-difluorophényl)-méthyl] thio]-7-[(3R)-pyrrolidin-3-ylamino]-thiazolo[4,5-d]pyrimidin-2(3H)-one,

destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

7. Utilisation d'un composé de formule (I) ou d'un sel ou d'un solvate pharmaceutiquement acceptable de celui-ci :



dans laquelle :

R¹ représente un groupement C₃-C₇ carbocyclique, C₁-C₈-alkyle, C₂-C₆-alcényle ou C₂-C₆-alcynyle, chacun des groupements étant éventuellement substitué par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, phényle, naphtyle ou un cycle aromatique ayant 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi N, S et O, les cycles phényle, naphtyle et aromatiques étant éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les atomes d'halogène, les groupements cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆-alkyle ou trifluorométhyle ; R² et R³ représentent, chacun indépendamment, un atome d'hydrogène ou un groupement C₃-C₇ carbocyclique, C₁-C₈-alkyle, C₂-C₆-alcényle ou C₂-C₆-alcynyle, ces quatre groupements pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi :

- (a) les atomes d'halogène, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -COOR⁷, -NR⁸COR⁹, -SR¹⁰, -SO₂R¹⁰, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹,
- (b) un cycle ayant 3 à 8 chaînons contenant éventuellement un ou plusieurs atomes choisis parmi O, S, NR⁸ et étant lui-même éventuellement substitué par C₁-C₃-alkyle ou halogène,
- (c) un groupement aryle ou un groupement

- hétéroaryle, chacun pouvant être éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les atomes d'halogène, les groupements cyano, nitro, -OR⁴, -NR⁵R⁶, -CONR⁵R⁶, -NR⁸COR⁹, -SO₂NR⁵R⁶, -NR⁸SO₂R⁹, C₁-C₆-alkyle et trifluorométhyle,
- R⁴ représente hydrogène, un groupement C₁-C₆-alkyle ou phényle, ces deux derniers pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, phényle, -OR¹¹ et -NR¹²R¹³;
- R⁵ et R⁶ représentent indépendamment un atome d'hydrogène ou un groupement C₁-C₆-alkyle ou phényle, ces deux derniers pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, phényle, -OR¹⁴ et -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, NR¹⁵SO₂R¹⁶, ou
- R⁵ et R⁶ forment, conjointement avec l'atome d'azote auquel ils sont liés, un système de cycles hétérocyclique saturé ayant 4 à 7 chaînons contenant éventuellement un hétéroatome supplémentaire choisi parmi les atomes d'oxygène et d'azote, ce système de cycles pouvant être éventuellement substitué par un ou plusieurs groupements substituants choisis indépendamment parmi phényle, -OR¹⁴, -COOR¹⁴, -NR¹⁵R¹⁶, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -SONR¹⁵R¹⁶, -NR¹⁵SO₂R¹⁶ ou C₁-C₆-alkyle, étant lui-même éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les atomes d'halogène et les groupements -NR¹⁵R¹⁶ et -OR¹⁷ ;
- R¹⁰ représente un atome d'hydrogène ou un groupement C₁-C₆-alkyle ou phényle, ces deux derniers pouvant être éventuellement substitués par un ou plusieurs groupements substituants choisis indépendamment parmi les atomes d'halogène, phényle, -OR¹⁷ et -NR¹⁵R¹⁶ ; et
- chacun de R⁷ R⁸ R⁹ R¹¹, R¹² R¹³, R¹⁴ R¹⁵, R¹⁶, R¹⁷ représente indépendamment un atome d'hydrogène ou un groupement C₁-C₆-alkyle ou phényle,
- dans la fabrication d'un médicament destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.
8. Utilisation d'un composé selon la revendication 1, **caractérisé en ce que** R¹ représente un groupement benzyle éventuellement substitué, dans la fabrication d'un médicament destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.
9. Utilisation d'un composé selon la revendication 1 ou la revendication 2, **caractérisé en ce que** l'un de R² et R³ est hydrogène et l'autre est C₁-C₆-alkyle substitué par hydroxy, dans la fabrication d'un médicament destiné à être utilisé dans la polyarthrite rhumatoïde.
10. Utilisation d'un composé selon la revendication 1, choisi parmi :
- la 7-[(2-hydroxy-1,1-diméthyléthyl)amino]-5-[(phénylméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la (R)-7-[[1-(hydroxyméthyl)propyl]amino]-5-[(phénylméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la (R)-7-[(2-hydroxy-1-méthyléthyl)amino]-5-[(phénylméthyl)thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hydroxy-1,1-diméthyléthyl)amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1R)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hydroxyéthoxy)éthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hydroxy-1-(hydroxyméthyl)éthyl)amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(2-hydroxyéthyl)amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la N-[2-[[5-[(2,3-difluorophényl)méthyl]thio]-2,3-dihydro-2-oxothiazolo[4,5-d]pyrimidin-7-yl]amino]éthyl]méthanesulfonamide,
- la (+/-)-5-[[2,3-difluorophényl)méthyl]thio]-7-[[2-(2-hydroxyéthoxy)-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 7-[(1R)-2-amino-1-méthyléthyl]amino]-5-[(2,3-difluorophényl)méthyl]thio]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1R)-2-(2-hydroxyéthyl)amino]-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1R)-2-(diméthylamino)-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[[4-(2-aminoéthoxy)-3-chlorophényl)méthyl]thio]-7-[(1R)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
- la 5-[[3-chloro-4-méthoxyphényl)méthyl]thio]-7-[(1R)-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,

la 5-[[3-chloro-2-fluorophényl)méthyl]thio]-7-
[[1*R*]-2-hydroxy-1-méthyléthyl] amino]thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2,3-difluorophényl)méthyl]thio]-7-[[3*R*,
4*R*]-4-hydroxypyrrolidin-3-yl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2,3-difluorophényl)méthyl]thio]-7-[(3*R*)-
pyrrolidin-3-ylamino]thiazolo[4,5-*d*]pyrimidin-2
(3*H*)-one,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[[2-méthyl-4-thiazoly] méthyl] thio] thiazolo [4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[2-hydroxy-1-(hydroxyméthyl)éthyl]amino]-5-
[[2-méthyl-4-thiazoly] méthyl] thio] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[(2-hydroxy-1,1-diméthyléthyl)amino]-5-
[[2-méthyl-4-thiazoly] méthyl] thio] thiazolo [4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[(2-hydroxy-1,1-diméthyléthyl)amino]-5-
[[2-méthylphényle] méthyl] thio] thiazolo [4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[(2-furanyl)méthyl]thio]-7-[[1*R*]-2-hydroxy-
1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2
(3*H*)-one,
la 7-[[1*R*]-2-amino-1-méthyléthyl]amino]-5-
[[3-chloro-2-fluorophényl)méthyl]thio] thiazolo [4,5-*d*]pyrimidin-2(3*H*)-one,
le (2*S*)-2-[[5-[[2,3-difluorophényl)méthyl]thio]-
2,3-dihydro-2-oxothiazolo [4,5-*d*] pyrimidin-7-
yl]-amino]-3-hydroxypropanamide,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[[2-thiénylemethyl]thio] thiazolo[4,5-*d*]pyrimidin-
2(3*H*)-one,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[[3-méthyl-4-(méthylsulfonyl) phényle] méthyl]
thio]-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[3-chloro-4-(trifluorométhoxy)phényle]méthyl]
thio]-7-[[1*R*]-2-hydroxy-1-méthyléthyl]-amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2-fluoro-3-(trifluorométhyl)phényle]méthyl]
thio]-7-[[1*R*]-2-hydroxy-1-méthyléthyl]-amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2,3-difluorophényl)méthyl]thio]-7-[2-[(di-
méthylamino) éthyl] amino] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 5-[(2-fluorophényle)méthyl]thio]-7-[[1*R*]-2-
hydroxy-1-méthyléthyl] amino] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[[2-méthoxyphényle] méthyl] thio] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[[2-phénoxyéthyl]thio] thiazolo[4,5-*d*]pyrimidin-
2(3*H*)-one,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[[3-méthylphényle] méthyl] thio] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 5-[(2-fluoro-3-méthylphényle)méthyl]thio]-7-

[[1*R*]-2-hydroxy-1-méthyléthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[3-chlorophényle)méthyl]thio]-7-[[1*R*]-2-
hydroxy-1-méthyléthyl] amino] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 5-[[3-bromophényle)méthyl]thio]-7-[[1*R*]-2-
hydroxy-1-méthyléthyl] amino] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 5-[[4-(difluorométhoxy)phényle]méthyl]thio]-
7-[[1*R*]-2-hydroxy-1-méthyléthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la (+/-)-5-[[2,3-difluorophényle)méthyl]thio]-7-
[[2-hydroxy-1-(méthoxyméthyl)éthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[2-hydroxy-1-(hydroxyméthyl)éthyl]amino]-5-
[(phénylemethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 5-[[2-bromophényle)méthyl]thio]-7-[[1*R*]-2-
hydroxy-1-méthyléthyl] amino] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 5-[[2,3-difluorophényle)méthyl]thio]-7-[[1*R*]-2-
hydroxy-1-méthyléthyl] amino] thiazolo [4,5-*d*]pyri-
midin-2(3*H*)-one,
la 5-[[3-chloro-2-fluorophényle)méthyl]thio]-7-
[[1*R*]-2-hydroxy-1-méthyléthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la (+/-)-5-[[2,3-difluorophényle)méthyl]thio]-7-
[[2-hydroxy-1-(méthoxyméthyl)éthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[2-hydroxy-1-(hydroxyméthyl)éthyl]amino]-5-
[(phénylemethyl)thio]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
la 7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]-5-
[(phénylemethyl)thio]thiazolo [4,5-*d*]pyrimidin-2
(3*H*)-one,
la 5-[(5-chloro-1,2,3-thiadiazol-4-yl)thio]-7-
[[1*R*]-2-hydroxy-1-méthyléthyl] amino] thiazolo-[4,5-*d*]pyrimidin-2(3*H*)-one,

et leurs sels et solvates pharmaceutiquement acceptables, dans la fabrication d'un médicament destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

45 11. Utilisation d'un composé selon la revendication 1, choisi parmi :

le sel sodique de 5-[[2,3-difluorophényle)méthyl]thio]-7-[[1*R*]-2-hydroxy-1-méthyléthyl] amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
le sel sodique de 5-[[3-chloro-2-fluorophényle)méthyl]thio]-7-[[1*R*]-2-hydroxy-1-méthyléthyl]amino]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-one,
le sel sodique de (+/-)-5-[[2,3-difluorophényle)méthyl]thio]-7-[[2-hydroxy-1-(méthoxyméthyl)éthyl] amino] thiazolo [4,5-*d*] pyrimidin-2 (3*H*)-one,
le sel sodique de 7-[[2-hydroxy-1-(hydroxyméthyl)éthyl]thio]-7-[[1*R*]-2-hydroxy-1-méthyléthyl] amino] thiazolo [4,5-*d*] pyrimidin-2(3*H*)-one,

thyl)-éthyl]amino]-5-[(phénylméthyl)thio]thiazolo-[4,5-d]pyrimidin-2(3H)-one, ou le sel sodique de 7-[(1R)-2-hydroxy-1-méthyl-éthyl] amino]- 5-[(phénylméthyl) thio] thiazolo-[4,5-d]pyrimidin-2(3H)-one,
dans la fabrication d'un médicament destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

12. Utilisation d'un composé selon la revendication 1, choisi parmi :

le trifluoroacétate de 7-[(1R)-2-amino-1-méthyl-éthyl] amino]- 5-[(2,3-difluorophényl) méthyl]thio]-thiazolo[4,5-d]pyrimidin-2(3H)-one,
le trifluoroacétate de 5-[(2,3-difluorophényl)-méthyl] thio]- 7-[(1R)- 2-[(2- hydroxyéthyl) amino]-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
la 5-[(2,3-difluorophényl)méthyl]thio]-7-[(1R)-2-(diméthylamino)-1-méthyléthyl]amino]thiazolo-[4,5-d]pyrimidin-2(3H)-one,
le trifluoroacétate de 5-[[4-(2-aminoéthoxy)-3-chlorophényl] méthyl] thio]- 7-[(1R)- 2- hydroxy-1-méthyléthyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one,
le monochlorhydrate de 5-[(2,3-difluorophényl)-méthyl] thio]- 7-[2-[(diméthylamino) éthyl] amino]-thiazolo[4,5-d]pyrimidin-2(3H)-one, ou le dichlorhydrate de 5-[(2,3-difluorophényl)-méthyl] thio]- 7-[(3R)-pyrrolidin- 3- ylamino]-thiazolo[4,5-d]pyrimidin-2(3H)-one,

dans la fabrication d'un médicament destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 9808847 A [0002]
- EP 0778277 A [0002]
- WO 9635678 A [0045]

Non-patent literature cited in the description

- Protective Groups in Organic Chemistry. Plenum Press, 1973 [0031]
- T. W. GREENE ; P. G. M. WUTS. Protective Groups in Organic Synthesis. Wiley-Interscience, 1991 [0031]
- *Indian J. Chem., Sect. B*, 1989, vol. 28B (11), 964-5 [0060]
- LEE et al. *J. Biol. Chem.*, 1992, vol. 267, 16293-16291 [0225]
- BALY et al. *Methods in Enzymology*, 1997, vol. 287, 70-72 [0227]
- MERRITT et al. *Biochem. J.*, 1990, vol. 269, 513-519 [0228]